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[Continued on next page]

(54) Title: NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE AND ACTIVITY IN MAMMALS

Percent Change in Plasma Proteins 12 hr post 2nd dose /pre-dose

				SU6668.004 BID (Tablets) Plasma/Pharmacokinetics for Day 1								
Pt #	SU6668 Dose (mg/m²)	cancer type	gender	SU6668 Cmax (ug/mL)	Tmax hrs	Exposure >2.3 ug/mL (hrs)	AUC ug*hr/mL	PAI-1	VEGF	MMP-9	TIMP-1	TF
28	400	prostate	M	13.0	15.0	21.3	164.3	297		46	27	21
32	300	ovarian	F	12.9	2.0	11.8	85.7	19	94	-45	-3	19
34	300	laryngeal	M	11.6	3.5	10.7	136.4	63	-1	156	-2	-5
17	200	colon	F	11.5	2.0	11.0	66.1	221			105	24
25	300	colon	M	11.0	2.0	13.4	75.5	7	-27	184	69	22
27	400	colon	M	10.3	6.0	9.1	71.2	-40	10	-15	-5	32
19	200	leiomyosarcoma	F	9.5	4.0	12.8	80.2	104	95	36	-0.2	-12
23	300	renal	F	9.3	2.0	8.0	53.5	-69	-36	-79	9	9
16	200	thyroid	F	9.3	2.0	7.3	55.7	263		409	43	37
24	300	leiomyosarcoma	F	8.2	4.0	16.4	71.2	62	9	18	-27	39
30	300	testicular	M	7.9	1.0	2.1	32.9	52	82	-66	13	-1
33	300	testicular	M	7.5	5.0	10.4	43.2	-20	121	305	99	212
31	300	hepatocellular	F	6.9	4.0	7.3	55.8	29	100	1	0	227
20	200	prostate	M	5.9	2.5	10.9	68.5	-47	181	48	-40	38
26	300	prostate	M	5.6	2.0	8.2	57.0	2	50	38	-21	-8
15	200	breast	F	5.3	2.0	4.8	44.0	95	11	-1	14	9
35	300	thyroid	M	4.3	1.5	16.1	97.5	-65	24	-19	64	65
22	300	colon	M	2.5	4.0	0.5	20.8	-14	28	29	-3	-5

	>500%
	29 to 500 %
	-66 to 28%

(57) Abstract: The present invention describes novel methods that measure in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one biomarker in a mammal exposed to a test compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine kinase activity.

WO 03/097854 A2

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

[0001] This application claims benefit of priority from U.S. provisional application Ser. Nos 60/380,872, filed May 17, 2002, 60/448,922, filed February 24, 2003, and 60/448,874, filed February 24, 2003, all of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] A biomarker is a molecular marker of a biological event or phenomenon in a organism. Changes in the level of certain biomakers indicate a biological response to a chemical compound in an organism. Biological responses include events at the molecular, cellular or whole organism level. Changes in biomarker levels can be measured and used to indicate whether or not a particular effect has been achieved in the organism. Changes in biomarker levels can indicate that an organism has been exposed to a particular compound. Changes in biomarker levels also can indicate whether an organism is experiencing or will experience a therapeutic effect or even a toxic event in response to a compound.

SUMMARY OF INVENTION

[0003] The present invention relates to novel methods comprising measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. In the novel methods, the level of at least one biomarker in a mammal exposed to a compound is compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound.

[0004] The invention includes methods for determining whether a test compound inhibits the activity of a protein tyrosine kinase. The invention further relates to methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also discloses methods for determining if a mammal is responsive to the administration of a compound that inhibits tyrosine kinase activity. In addition, the invention relates to methods for identifying mammals that will respond therapeutically to a compound that inhibits VEGFR and/or PDGFR tyrosine kinases. The invention further discloses methods for testing or predicting, as well as kits for determining, whether a mammal will respond therapeutically to a compound that inhibits tyrosine kinase activity. The invention also relates to methods for testing or predicting whether a mammal

will experience an adverse event, such as fatigue, in response to a method of treatment comprising adminstering a compound that inhibits tyrosine kinase activity.

[0005]

BRIEF DESCRIPTION OF THE FIGURES

[0006] Figure 1 shows the levels of various plasma proteins in plasma from human patients, measured by ELISA, before and 24 hours after the first dose of Compound A (SU6668).

[0007] Figure 2 shows the abundance of a protein (spot #5) in patient plasma, measured by 2D polyacrylamide gel analysis, before and 4 hours after the first dose of Compound A (SU6668).

[0008] Figure 3 shows the identification by mass spectrometry analysis of spot #5 from the 2D gel analysis of patient plasma analyzed in Figure 2.

[0009] Figure 4A shows the change in level of various RNA transcripts, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis. Figure 4B shows the change in the level of vinculin RNA, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis.

[0010] Figure 5 shows the levels of various RNA transcripts, in patient blood samples, on treatment day 28 (27 days after the first dose of Compound A) versus the levels on treatment day 0 (before treatment with Compound A). Numbers shown indicate increase and/or decrease relative to baseline on day 0. No significant change is shown as ~1. Levels decreased are less than 1 and levels increased are greater than 1.

[0011] Figure 6 shows the differential expression of candidate biomarker transcripts in patient PBMC at day 56 relative to day 1 of therapy. The diagram is a depiction of the Affymetrix Difference Calls assigned to each day 56:day 1 expression comparison among the patient sample pairs analyzed via GeneChip hybridization analysis. Letters within blocks represent the Difference Call assigned to each relative expression comparison. The abbreviations are: I = Increase, MI = Marginally Increased, NC = Not Changed; MD = Marginally Decreased; D = Decreased. Cases in which an Increased or Marginally Increased call is assigned to a day 56:day 1 comparison are shaded in gray. Each column represents a different patient. Column headings in each grid represent patient response assessed at the end

of first treatment cycle: PR = partial response, CR = complete response, PD = progressive disease.

[0012] Figures 7A and 7B show the percentage of patients with increased expression of biomarker transcripts following treatment with Compound B (SU5416). Differential expression of six transcripts as measured by microarray and quantitative RT-PCR is presented. The percentage of cases in 5-FU/LV (control) and 5-FU/LV + SU5416 trial arms with increased expression (at predose day 56 relative to predose day 1) of each transcript is displayed. Figure 7A shows the results of the Affymetrix analysis and Figure 7B shows the results from SYBR Green RT-PCR. For the SYBR Green data, an increased is defined as relative expression value of 2-fold or greater. A total of 31 sample pairs were used in RT-PCR analysis; 18 were from SU5416 arm (5 PR, 1 CR, 11 PD and 1 SD response at end of cycle 1), and 13 were from the control arm (9 PR, 3 PD and 1 SD).

[0013] Figure 8 shows the percentage of patients with increased expression of four biomarker transcripts, following treatment with Compound B (SU5416). Differential expression of four transcripts as measured by quantitative RT-PCT is presented. Percentage of cases in CPT-11/5-FU/LV (control) and CPT-11/5-FU/LV + SU5416 trial arms with increased expression (at predose day 42 relative to predose day 1) of four candidate biomarker transcripts in a second SU5416 Phase III clinical trial is displayed. The convention is the same as in panel B in Figure 7. A total of 36 sample pairs was included in this analysis; 18 from the Compound B arm and 18 from the control arm (8 PR and 10 SD responses at end of cycle 1 in each group).

[0014] Figure 9 shows hierarchical clustering of relative expression ratios for four biomarker transcripts. This mosaic depicts association between patent samples and relative expression of the four potential biomarker transcripts. Natural log-transformed SYBR Green RT-PCR ratio data (relative expression of day 56:day 1) were used in analysis. In the color scheme, higher ratios are indicated in red, lower ones in green (scale ranges from –4 to +4). Results from individual patients are oriented as rows and transcripts are oriented as columns. Red bars on the right side of the map indicate cases from the SU4316 arm. The hierarchical clustering method is average linkage and the distance metric is Euclidean.

[0015] Figure 10 shows PAI-1 levels on day 1 and day 56 in patient plasma samples. MR = minor response (cycle 1); PR = partial response (cycle 1); PD = progressive disease (cycle 1)

[0016] Figure 11 shows the mRNA and protein sequences for lactoferrin (SEQ ID NOS 68-69, respectively), lipocalin-2 (SEQ ID NOS 70-71 and 180, respectively), MMP9 (SEQ ID NOS 72 & 66, respectively), and CD24 (SEQ ID NO: 73-74, respectively).

[0017] Figure 12 shows mRNA and protein sequences for eucaryotic initiation factor 4A11 (SEQ ID NOS 75-76, respectively), human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792) (SEQ ID NOS 77-78, respectively), Homo sapiens thymosin beta-10 (SEQ ID NOS 79-80, respectively), Homo sapiens hnRNPcore protein A1 (SEQ ID NOS 81-82, respectively), human leucocyte antigen (CD37) (SEQ ID NOS 83-84, respectively), human MHC call II HLA-DR beta-1 (SEQ ID NOS 85-86, respectively), Homo sapiens translation initiation factor elF3 p66 subunit (SEQ ID NOS 87-88, respectively), Homo sapiens nm23-H2 gene (SEQ ID NOS 89-90, respectively), human acidic ribosomal phosphoprotein P0 (SEQ ID NOS 91-92, respectively), human cyclophillin (SEQ ID NOS 93-94, respectively), Genbank Accession No. AI541256 (cDNA) (SEQ ID NO: 95), human T-cell receptor active beta chain (SEQ ID NOS 96-97, respectively), human MHC class II lymphocyte antigen (HLA-DP) beta chain (SEQ ID NOS 98-99, respectively), human KIAA0195 (SEQ ID NOS 100-101, respectively), Homo sapiens MAP kinase kinase 3 (MKK3) (SEQ ID NOS 102-103, respectively), human beta-tubulin class III isotype (beta-3) (SEQ ID NOS 104-105, respectively), human tropomyosin (SEQ ID NOS 106-107, respectively), 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C (SEQ ID NOS 108-109, respectively), human MLC emb gene for embryonic myosin alkaline light chain (SEQ ID NOS 110-111, respectively), Homo sapiens glyoxalase II (SEQ ID NOS 112-113, respectively), Homo sapiens trans-golgi network glycoprotein 48 (SEQ ID NOS 114-115, respectively), histone H2B (SEQ ID NOS 116-117, respectively), human RLIP76 protein (SEQ ID NOS 118-119, respectively), Genbank Accession No. W26677 (human retina cDNA) (SEQ ID NO: 120), human PMI gene for a putative receptor protein (SEQ ID NOS 121-122, respectively), human DNA-binding protein A (dbpA) (SEQ ID NOS 123-124, respectively), human ITIH4 (SEQ ID NOS 125-126, respectively), IL-8 (SEQ ID NOS 182-183, respectively) and C-reactive protein (SEQ ID NOS 184-185, respectively).

[0018] Figure 13 shows the changes in VEGF plasma levels, as measured by ELISA, in patients receiving a malate salt of Compound 1 in Trial C.

[0019] Figure 14 shows by hybrid ELISA that VEGF/PLGF heterodimers are detected in plasma of cancer patients and are induced in patients after treatment with a malate salt of Compound 1 in Trial C. The hybrid ELISA assay demonstrates that levels of

heterodimers are increased in 3 of 3 patients tested, and follow a pattern of induction similar to that seen for VEGF and PLGF.

[0020] Figure 15 shows that plasma levels of soluble VEGFR2 decrease in patients in Trial D following treatment with a malate salt of Compound 1 in a dose-dependent manner.

[0021] Figure 16 shows that the decrease in sVEGFR2 following treatment with Compound 1 or malate salt thereof correlates with AUC values (end of C1 dosing, all trials). The scatter graph plots sVEGFR2 fold change (end of cycle 1 dosing over baseline) against AUC values from end of cycle 1 dosing. Results from the first 44 patients (representing 4 trials) are included.

[0022] Figure 17 shows that chemokine MIG is induced in patients during treatment with a malate salt of Compound 1. MIG is a biomarker that also correlates with tumor responses as measured by ^{18}FDG-PET imaging. Results are from Trial C.

[0023] Figure 18 discloses the amino acid sequence of human vascular endothelial growth factor (VEGF) (SEQ ID NO: 127).

[0024] Figure 19 discloses the amino acid sequence of human placenta growth factor (PLGF) (SEQ ID NO: 128).

[0025] Figure 20 discloses the amino acid sequence of human vascular endothelial growth factor receptor 2 (VEGFR2) (SEQ ID NO: 129).

[0026] Figure 21 discloses the amino acid sequence of human Monokine Induced by Interferon-Gamma (MIG) (SEQ ID NO: 55).

[0027] Figure 22 discloses the amino acid sequence of human interferon-inducible cytokine IP-10 (SEQ ID NO: 130).

[0028] Figure 23 discloses the amino acid sequence of human Interferon-inducible T-cell alpha chemoattractant (I-TAC) (SEQ ID NO: 131).

[0029] Figure 24 shows cDNA or mRNA sequences for human vinculin (SEQ ID NOS 132 & 181, respectively), basic transcription factor 3 homologue (SEQ ID NO: 133), human c-jun proto oncogene (SEQ ID NO: 134), human c-fos proto-oncogen (SEQ ID NO: 135), Homo sapien PTP-nonreceptor type 2 (SEQ ID NO: 136), human cdc2-related protein kinase (SEQ ID NO: 137), human cyclin C (SEQ ID NO: 138), human DNA polymerase-gamma (SEQ ID NO: 139), protein kinase C-alpha (SEQ ID NO: 140), lipocortin II/annexin

A2 (SEQ ID NO: 141), histone H2B member R (SEQ ID NO: 142), Homo sapien amphiregulin (SEQ ID NO: 143), human basic transcription factor 3 (SEQ ID NO: 144), Homo sapien phosphoinositide-3-kinase p110 subunit (SEQ ID NO: 145), human gelsolin (SEQ ID NO: 146), Homo sapien Cyclin D2 (SEQ ID NO: 147), ephrin receptor (EphB4) (SEQ ID NO: 148), human Hanukah factor/granzyme A (SEQ ID NO: 149), von Hippel-Lindau (VHL) tumor suppressor (SEQ ID NO: 150), human mRNA for OB-cadherin-1 (SEQ ID NO: 151), human mRNA for OB-cadherin-2 (SEQ ID NO: 152), phosphoinositol 3-phosphate-binding protein-3 (PEPP3) (SEQ ID NO: 153), human phosphoinositol 3-kinase p85 subunit (SEQ ID NO: 154), human mucin 1 (SEQ ID NO: 155), ErbB3/HER3 receptor tyrosine kinase (SEQ ID NO: 156), and Homo sapien gene for hepatitis C-associated microtubulear aggregate protein p44 (nine exons) (SEQ ID NOS 157-164, respectively).

[0030] Figure 25 shows that FLT3 ligand (FL) is induced in patients during treatment with Compound 1.

[0031] Figure 26 demonstrates that interleukin-6 (IL-6) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in IL-6 plasma concentration after treatment with Compound 1 corrolates with patient fatigue.

[0032] Figure 27 demonstrates that C-reactive protein (CRP) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in CRP plasma concentration after treatment with Compound 1 corrolates with patient fatigue.

[0033] Figure 28 shows that a higher baseline value of CRP in patients with GIST corrolates with progressive disease, in Trial D.

[0034] Figure 29 shows that protein expression of OB-cadherin 1 (cadherin 11) is up-regulated in Colo205 xenograph tumors after exposure to Compound 1 for 24 or 48 hours.

BRIEF DESCRIPTION OF THE TABLES

[0035] Tables 1-22 appear following the Examples disclosed in this application, and specifically after Section K.

[0036] Table 1 shows Compound B (SU5416) PBMC sample processing history for Trial A.

[0037] Table 2 shows a list of biomarker transcripts as detected in Affymetrix analysis.

[0038] Table 3 shows primer sequences used in RT-PCR validation analysis.

[0039] Table 4 shows a Mann-Whitney U Test comparison of expression fold change data from Compound B and control arms (Trial A). This statistical analysis was performed to assess the significance of differences in expression change ratios (day 56 vs day 1) between the Compound B and control arms. Separate comparisons were performed of expression change values from Affymetrix analysis and from SYBR Green RT-PCR validation experiments. P-values ≤ 0.05 were considered statistically significant.

[0040] Table 5 shows the Mann-Whitney U Test of Compound B expression data in Trial B.

[0041] Table 6 shows a summary of class prediction results for pooled data (3 gene predictor set).

[0042] Table 7 shows changes in plasma levels of PLGF in patients in Trial C receiving daily treatment with a malate salt of Compound 1.

[0043] Table 8 shows changes in plasma levels of MIG, IP-10, and I-TAC in patients receiving treatment with Compound 1 or a malate salt thereof. Levels of IP-10 and I-TAC at end cycle 1 dosing are estimated values in some cases (>500), as the amount of IP-10 or I-TAC in these samples was higher than the highest standard provided for standard curve generation. All patients represented in this table are from Trial C, except for patient 11 from Trial B and patient 9 from Trial A. Patients in Trial C received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0044] Table 9 shows changes in PLGF and/or sVEGFR2 plasma levels in cancer patients after receiving treatment with Compound 1 or a malate salt thereof. For PLGF, italics text indicates a fold-change of 3-fold or greater, end of cycle 1 dosing relative to day 1. For sVEGFR2, italics text indicates a decrease of 30% or more, end of cycle 1 dosing relative to day 1. Patients in Trials C and D received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0045] Table 10 shows an increase in MIG plasma levels in cancer patients after receiving treatment with Compound 1 or malate salt thereof. As with Table 2, results are from Trial C except for patient 11 from Trial B and patient 9 from Trial A..

[0046] Table 11A shows the change in levels of various mRNA transcripts isolated from Colo205 xenograft tumors, as measured by DNA Array analysis, before exposure to Compound 1, and 6 hours and 24 hours after exposure to the first dose of Compound 1.

[0047] Table 11B shows the change in levels of various mRNA transcripts isolated from SF767 xenograft tumors, measured by DNA Array analysis, before exposure to Compound 1, and 4 hours and 24 hours after exposure to the first dose of Compound 1.

[0048] Table 12 shows the change in the levels of protein expression and/or mRNA transcript abundance in Colo205 xenograft tumors, as measured by Taqman Real Time PCR, before exposure to Compound 1, and at 6 hours versus 24 hours after exposure to the first dose of Compound 1. The following transcripts were measured: Amphiregulin, Cdc2-related protein kinase, phosphoinositol 3-kinase, p110 subunit, cyclin C, OB-Cadherin1, OB-Cadherin2, p85 subunit, Mucin 1, von Hippel-Lindau (VHL) tumor suppressor, ephrin recetor (EphB4), and Gelsolin.

[0049] Table 13 shows the forward and reverse primer and probe sequences used in the TaqMan Real Time PCR Analysis of Colo205 xenograft tumor samples.

[0050] Table 14 lists three sets of 2D gels used in MALDI-TOF-MS and MALDI-MS/MS analysis.

[0051] Table 15 shows the quantification of Spot #1202 from 2D gel analysis. 2D gel analysis was performed on samples isolated from HUVECs that were stimulated with VEGF after pre-treatment with Compound 1 or vehicle control (DMSO).

[0052] Table 16 shows definitive identification of Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-TOF-MS analysis.

[0053] Table 17 identifies Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-MS/MS analysis.

[0054] Table 18 shows quantitative ELISA analysis of pro-MMP1 levels in HUVEC conditioned media, after stimulatation of HUVEC cells with VEGF after pre-treatment with Compound 1 at 10 nM, 100 nM or 1 μM concentrations, or vehicle control (DMSO).

[0055] Table 19 shows an increase pro-MMP1 levels in patient plasma after treatment with Compound 1. Results are from Study B.

[0056] Table 20 lists the analytes measured using Array 1.1 and Array 2.1 in an antibody chip microassay analysis.

[0057] Table 21 lists 23 biomarkers that show changes in plasma levels following treatment with Compound 1. An up arrow, down arrow or (-) denote relative increase, decrease or no change in detected level respectively, in samples for patients 1, 2 and 3. The

accession numbers for markers, not previously described herein, are as follows: ENA-78 (epithelial derived neutrophil activating protein 78) (SEQ ID NO: 48), P42830; MPIF-1 (myeloid progenitor inhibitory factor 1) (SEQ ID NO: 49), P55773; GCP-2 (gamma tubulin complex component 2) (SEQ ID NO: 50), Q9BSJ2; Amphiregulin (Amphireg) (SEQ ID NO: 51), AAA51781; IL-1α (interleukin-1 alpha) (SEQ ID NO: 52), NP 000566 for preprotein; IL-1β (interleukin-1 beta) (SEQ ID NO: 53), NP000567 for preprotein; IL-2 (interleukin-2) (SEQ ID NO: 54), NP000577 for preprotein; MIG (mitogen inducible gene) (SEQ ID NO: 55), NP 061821; NT4 (neurotrophin 4/neurotrophic factor 5) (SEQ ID NO: 56), NP 006170; IGFBP-1 (insulin-like growth factor binding factor-1) (SEQ ID NO: 57), NP 000587; GRO-β (SEQ ID NO: 58), AAA63183; TNFR1 (tumor necrosis factor receptor 1) (SEQ ID NO: 59), P19438; FLT3 ligand (fms-like tyrosine kinase ligand/Flk 2 ligand) (SEQ ID NO: 60), I38440; IL-6 (interleukin-6) (SEQ ID NO: 61), NP-000591; MCP-1 (monocyte chemoattractant protein 1) (SEQ ID NO: 62), P13500; TNFα (tumor necrosis factor alpha) (SEQ ID NO: 63), NP 000585; TARC (thymus and activation regulated chemokine) (SEQ ID NO: 64), Q92583; MMP7 (SEQ ID NO: 65), NP 002414 for preprotein; MMP9 (SEQ ID NO: 66), NP 004985 for preprotein; and leptin (SEQ ID NO: 67), NP000221 for preprotein. Note that accession numbers and SEQ ID NOs in this specification are used to identify cDNAs, mRNAs or proteins of interest, rather limit the biomarkers to specific sequences.

[0058] Table 22 shows the relative fold change of six plasma biomarkers in three patients (denoted 1, 2 and 3) following Compound 1 treatment relative to predose, as measured by two methods: ELISA; and antibody chip technology (MSI).

DETAILED DESCRIPTION OF THE INVENTION

[0059] The present invention relates to novel methods for determining whether a test compound inhibits tyrosine kinase activity and novel methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also relates to novel methods for determining whether a mammal is experiencing or will experience a particular biological phenomenon, such as a therapeutic effect, "responding" (as defined herein), or an adverse event, in response to a compound that inhibit tyrosine kinase activity.

[0060] The novel methods comprise measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one

biomarker in the mammal exposed with a test compound, as compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The tyrosine kinases of the novel methods include, but are not limited to, those selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor.

[0061] In certain embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone, as described herein, and also in U.S. Serial No. 10/281,266. In other embodiments, the tyrosine kinase inhibitor comprises compounds described in U.S. Ser. No. 09/783,264, WO 01/60814, U.S. Ser. No. 10/076,140, U.S. Ser. No. 10/281,266, U.S. Ser. No. 10/281,985, U.S. Ser. No. 10/237,966 (now a U.S. provisional application), as well as a U.S. provisional application Ser. No. 60/448,861, filed February 24, 2003 (entitled "Treatment of excessive osteolysis with indolinone compounds"), all of which are hereby incorporated by reference.

[0062] Identification of biomarkers that provide rapid and accessible readouts of efficacy, drug exposure, or clinical response is increasingly important in the clinical development of drug candidates. Embodiments of the invention include measuring changes in the expression levels of secreted proteins, or plasma markers, which represent one category of biomarker. In one embodiment, plasma samples, which represent a readily accessible source of material, serve as a surrogate tissue for biomarker analysis.

A. Definitions

[0063] Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below.

[0064] "Test compound" refers to any pharmaceutical composition that inhibits or modulates a protein tyrosine kinase.

[0065] "Tyrosine kinase modulator" or "tyrosine kinase inhibitor" refers to any chemical composition that modulates, affects, alters, inhibits or reduces the enzymatic activity or tyrosine phosphation action of a tyrosine kinase.

B. Biomarkers Modulated in Mammals Exposed to Tyrosine Kinase Inhibitors

[0066] In one embodiment, the invention includes a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

[0067] Alternatively, a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

[0068] In an other embodiment, the invention includes a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated

microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

[0069] Alternatively, a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative

receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

[0070] In an other embodiment, the invention includes a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0071] Alternatively, a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase

precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0072] In another embodiment, the invention includes a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1,

GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal is responding to the compound that inhibits tyrosine kinase activity.

[0073] Alternatively, a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic

transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

[0074] The term "responding" encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect or an adverse event), in a mammal.

[0075] In another embodiment, the invention includes a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation

initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0076] In another embodiment, the invention includes a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in a same type of mammal without cancer the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the

mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0077] As used throughout the specification, the term "respond therapeutically" refers to the alleviation or abrogation of a disease, such as cancer. This term means that the life expectancy of an individual affected with the disease will be increased or that one or more of the symptoms of the disease will be reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known known in the art, such as PET imaging.

[0078] In another embodiment, the mammal is a human. In other embodiments, the mammal is a rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate, or monkey.

[0079] In other embodiments, any of the proceeding methods is an in vitro method, and the protein and/or mRNA biomarker is measured in at least one mammalian biological tissue. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological fluid, including but not limited to whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological tissue including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

[0080] In yet other embodiments, the methods of the invention are carried out on mammals who have cancer. The cancer can be, for example, but is not limited to, prostate cancer, colorectal cancer (CRC), thyroid cancer, an advanced solid malignancy, pancreatic cancer, breast cancer, parotid cancer, synovial cell cancer or sarcoma, gastrointestinal stromal tumor (GIST), laryngeal cancer, testicular cancer, leiomyosarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, ovary cancer, lung cancer, colon cancer, renal cell carcinoma, sarcoma, retropero sarcoma, pelvis sarcoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, neuroendocrine cancer, bronchial adenocarcinoma, head and neck cancer and/or thymic cancer.

[0081] In other embodiments, any of the preceeding methods also comprise a step wherein the mammal is also exposed to a cancer chemotherapeutic agent before, during and/or after exposure to the compound that inhibits tyrosine kinase activity.

[0082] Other embodiments also include any of the proceeding methods, wherein the "difference" refers to an increase in the level of at least one of the following protein(s) and/or

mRNA transcript(s): PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGR/PLGR heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2B, human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ephrin receptor EphB4, OB-cadherin 1, phosphoinositol 3-kinase p85 subunit, mucin 1 and gelsolin, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0083] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of prostate cancer, colon cancer, thyroid cancer and an advance solid malignancy, and wherein the "difference" refers to an increase in the level of VEGF protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of VEGF protein and/or mRNA transcript as measured before exposure to the compound.

[0084] Other embodiments also include any of the proceeding methods wherein the mammal has colon or colorectal cancer, and wherein the "difference" refers to an increase in the level of at least one of VEGF, MMP-9, lactoferrin, lipocalin-2, and/or CD24 antigen protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0085] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of synovial sarcoma, rectal cancer, gall-bladder cancer,

hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, colon cancer, renal cell carcinoma, sarcoma, retropero sarcoma, pelvis sarcoma, parotid cancer, uterine cancer, pelvic angiosarcoma, colorectal cancer and gastrointestinal stromal tumor (GIST), and wherein the "difference" refers to an increase in the level of at least one of VEGF, PLGF and VEGF/PLGF heterodimers protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0086] Other embodiments also include any of the proceeding methods wherein the mammal has an advanced solid malignancy, and wherein the "difference" refers to an increase in the level of VEGF and/or MMP-9 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0087] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of pancreatic cancer, synovial sarcoma, colon cancer, non-small cell lung cancer (NSCLC), rectal cancer, pelvis sarcoma, and sarcoma and/or bronchial adenocarcinoma, and wherein the "difference" refers to an increase in the level of at least one of MIG, IP-10 and I-TAC protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0088] Other embodiments also include any of the proceeding methods wherein the mammal has thryoid cancer, and wherein the "difference" refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophillin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2b and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0089] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the "difference" refers to an increase in the level of at least one of eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0090] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the "difference" refers to an increase in the level of at least one of human acidic ribosomal phosphoprotein P0, human cyclophillin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0091] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the "difference" refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0092] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the "difference" refers to an increase in the level of at least one of Homo sapiens thymosin beta-10 gene, Homo sapiens MAP kinase kinase 3

(MKK3) and histone H2B member R protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0093] Other embodiments also include any of the proceeding methods wherein the mammal has synovial cell cancer, and wherein the "difference" refers to an increase in the level of human RLIP76 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of human RLIP76 protein and/or mRNA transcript as measured before exposure to the compound.

[0094] Other embodiments also include any of the proceeding methods, wherein the "difference" refers to a decrease in the level of at least one of the following protein(s) and/or mRNA transcript(s): ITIH4, PAI-1, soluble VEGF receptor 2 (sVEGFR2), Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78, MPIF-1, MMP7, MIG, cdc2 related protein kinase, and phosphoinositol 3-kinase p110 subunit, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0095] Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of breast cancer, prostate cancer and thyroid cancer, and wherein the "difference" refers to a decrease in the level of ITIH4 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of ITIH4 protein and/or mRNA transcript as measured before exposure to the compound.

[0096] Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of synovial sarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, melanoma, colon cancer, renal cell carcinoma, non-small cell lung cancer (NSCLC), sarcoma, retropero sarcoma, pelvis sarcoma, squamous cell carcinoma parotid cancer, bronchial adenocarcinoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, colorectal cancer (CRC), neuroendocrine cancer, gastrointestinal stromal tumor (GIST), head and neck cancer, thymic cancer and thyroid cancer, and wherein the "difference" refers to a decrease in the level of sVEGFR2 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of sVEGFR2 protein and/or mRNA transcript as measured before exposure to the compound.

[0097] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the "difference" refers to a decrease in the level of at least one of Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human beta-tubulin class III isotype (beta-3), and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0098] Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the "difference" refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0099] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the "difference" refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo

sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0100] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the "difference" refers to a decrease in the level of at least one of human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0101] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the "difference" refers to a decrease in the level of at least one of human KIAA0195, Homo sapiens trans-golgi network glycoprotein 48, histone H2B and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0102] In another embodiment, the invention also includes a kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic

ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

[0103] In another embodiment, the invention also includes the preceeding kit, wherein the instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens

cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

[0104] wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

[0105] In another embodiment, the invention also includes a method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

[0106] As used in the specification, the term "adverse event" refers to a physiological effect in a mammal, such as fatigue or other side effect, that is severe enough to warrent altering, reducing or eliminating the mammal's exposure to a particular tyrosine kinase inhibitor. Exposure or adminstration can be altered, reduced or eliminated in terms of the amount or dosage of the tyrosine kinase inhibitor, as well as length of time and/or frequency of exposure. A determination as to whether a particular physiological effect is severe enough to be considered "an adverse event" falls within the judgment of those skilled in the art, such as a laboratory scientist, veterinarian or medical practitioner.

C. Further Embodiments of the Novel Methods

1. Measurement of Protein and mRNA

[0107] In other embodiments, the novel methods of Section B are carried out so that the step where the mammal is exposed to test compound includes administration of at least one dose of test compound, or at least two doses, or at least 5 doses or at least 10 doses, up to at least 55 or 56 doses. In certain embodiments, these doses are administered during a period of 4 hours, 6 hours, or 24 hours to about 100 days. In further embodiments, the doses are administered over a period of 24 hours, 2 days, or 28 days. In other embodiments, two doses are administered per every 24 hours, and in other embodiments, the doses are administered about every 12 hours. It will be understood by those of skill in the art that the administration of test compound, according to the exposure steps of the methods of Section B, can be varied to suit individual needs of the mammal being treated, the compound being administered, the method of administration and the disease being treated. For example, in a typical dosing regimen, the patient receives one dose per day of test compound, for a number of days, such

as about 28 or about 56 days. In other dosing regimens, the test compound is administered about once per day, twice per week, or once per week.

[0108] The measurement of protein and/or RNA, following the exposure step in the methods of Section B, can be carried out on a sample from the mammal taken about 4 or 6 hours following the first dose (exposure) of the mammal to test compound. In other embodiments, this measurement is carried out on a sample taken 12 hours, 1 day, 2 days, up to about 100 days, after the first dose (exposure) of the mammal to test compound. In other embodiments, the protein and/or mRNA measurements are taken from samples from the mammals 4 or 6 hours after the first dose of test compound or 24 hours after the first dose of test compound, or 15 or 28 days after the first dose of test compound. Typically, dosing of test compound will be periodic between the first and last dose of test compound that precedes the sample taken for measurement of biomarker protein and/or mRNA. For example, the test compound is administered once a day, every day for 28 days. Typically, the mammal sample taken (for measurement of biomarker protein and/or mRNA) will be taken shortly following the most recent dose of test compound, for example within 24 of the most recent dose of test compound.

[0109] In other embodiments, the methods of Section B are carried out so that the measurement of protein and/or mRNA is carried out on a mammalian tissue selected from biological fluids, including but not limited to the group of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, and other tissues including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue, bone marrow.

[0110] In other embodiments, the methods of Section B are carried out on a mammal that is further exposed to other chemotherapeutic agents, including but not limited to 5-fluoro-uracil (5-FU), leucovorin, CPT11, aromasin, taxol, paclitaxel, other "standard of care" agents used in patients, COX-2 inibitors (such as celecoxcib), and other tyrosine kinase inhibitors. Such exposure to a cancer chemotherapeutic agent can be before, during and/or after exposure to test compound.

[0111] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least

25%. In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 2-, 3-, 5-, 10-, 15- or 24-fold. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5-, 4.0-, 4.2-, 4.5-, 5.0-, 5.5-, 6.0-, 6.1-, 6.5-, 7.0-, 7.3-, 10.0-, 15.0-, 19.0- or 24-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 1.7- or 2.0-fold.

[0112] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 25%. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least 1.3-, 1.4-, 1.5-, 1.6-,1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5- , 3.0-, 3.5- or 3.7-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 1.7- or 2.0-fold.

[0113] To quantify the protein and/or mRNA measured in the novel methods of Section B, methods well known to the skilled artisan are used. For example, quantification of protein can be carried out using methods such as ELISA, 2-dimensional SDS PAGE, Western Blot, immunoprecipitation, immunohistochemistry, fluorescense activated cell sorting (FACS), fow cytometry. Quantification of mRNA is measured using methods such as PCR, array hybridization, Northern blot, in-situ hybridization, dot-blot, Taqman, RNAse protection assay.

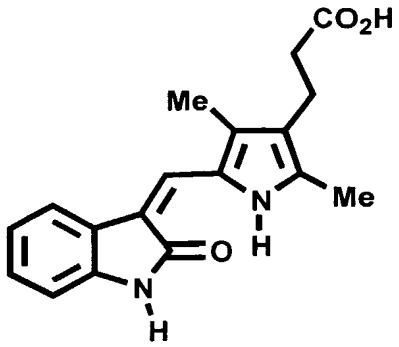
[0114] In further embodiments of the invention, the methods of Section B are carried out so that the level of at least two, or at least three, or at least four, or at least five, or at least 6, or at least seven or at least eight, or at least nine, up to 87 of the biomarkers are measured in a mammal. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 66 biomarkers of Section B that are increased upon exposure of a mammal to a compound that inhibits tyrosine kinase. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 39 biomarkers of Section B that are decreased upon exposure of a mammal to a compound that inhibits tyrosine kinase.

2. Tyrosine Kinase and Inhibitors of Tyrosine Kinase

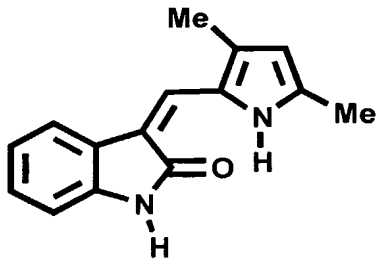
[0115] In certain embodiments, the tyrosine kinases of the novel methods are selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor. See, for example, U.S. Pat. No. 6,177,401 (Flk-1), WO 01/45689 (c-kit), GenBank Accession No. NM 002609 (PDGFR-beta), GenBank Accession No. NM 006206 (PDGFR-alpha), GenBank Accession No. NM 023109 (FGFR-1), GenBank Accession No. NM 023028 (FGFR-2) and GenBank Accession No. NP_005202 (c-fms/CSF-1 receptor).

[0116] FLT3 (fms like tyrosine kinase 3) is a member of the class III receptor tyrosine kinases. Those of skill in the art will recognize that FLT3 has also been called "flk2" in the scientific literature. "FLT3" as used herein, refers to a polypeptide having, for example, the sequence set forth in accession number gi|4758396|ref|NP_004110.1| fms-related tyrosine kinase 3 [Homo sapiens], or gi|544320|sp|P36888|FLT3_HUMAN FL CYTOKINE RECEPTOR PRECURSOR (TYROSINE-PROTEIN KINASE RECEPTOR FLT3) (STEM CELL TYROSINE KINASE 1) (STK-1) (CD135 ANTIGEN), or gi|409573|gb|AAA18947.1| (U02687) serine/threonine protein kinase [Homo sapiens]. Corresponding mRNA accessions for the first two sequences are gi|4758395|ref|NM_004119.1| Homo sapiens fms-related tyrosine kinase 3 (FLT3), mRNA gi|406322|emb|Z26652.1|HSFLT3RTK H.sapiens FLT3 mRNA for FLT3 receptor tyrosine kinase.

[0117] In other embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone compound. In another embodiment, the test compound is a compound of Formula I. These, and other exemplary tyrosine kinase inhibitors, are shown below. The skilled artisan will recognize that the novel methods of the invention can be used to test any tyrosine kinase inhibitor, in addition to those listed below.



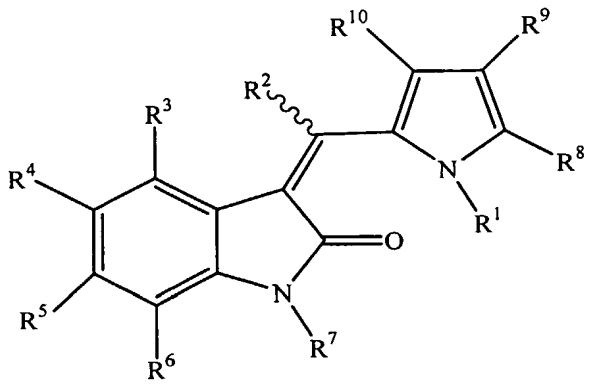
[0118] Compound A (SU6668): 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.



[0119] Compound B (SU5416): 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one.

[0120]

A pyrrole substituted 2-indolinone having the formula:



wherein:

R^1, R^2 and R^7 are hydrogen;

R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

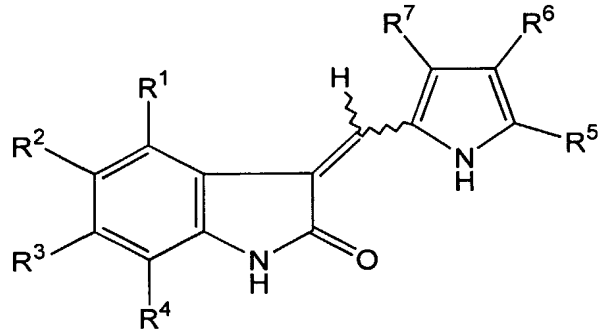
R^8 is unsubstituted lower alkyl;

R^9 is $-(CH_2)(CH_2)C(=O)OH$; and

R^{10} is unsubstituted lower alkyl.

[0121]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cyclkoalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_rR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14}$, $-S(O)_2NR^{13}R^{14}$,

$-NR^{13}C(O)R^{14}$,

$-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5, R^6 or R^7 must be $-C(O)R^{10}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl and aryl;

R^{10} is selected from the group consisting of hydroxy, alkoxy, aryloxy, -$N(R^{11})(CH_2)_nR^{12}$, and -$NR^{13}R^{14}$;

R^{11} is selected from the group consisting of hydrogen and alkyl;

R^{12} is selected from the group consisting of -$NR^{13}R^{14}$, hydroxy, -$C(O)R^{15}$, aryl, heteroaryl, -$N^+(O^-)R^{13}R^{14}$, -$N(OH)R^{13}$, and -$NHC(O)R^a$ (wherein R^a is unsubstituted alkyl, haloalkyl, or aralkyl);

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^{13} and R^{14} may combine to form a heterocyclo group;

R^{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R^{16} is selected from the group consisting of hydroxy,

-$C(O)R^{15}$, -$NR^{13}R^{14}$ and -$C(O)NR^{13}R^{14}$;

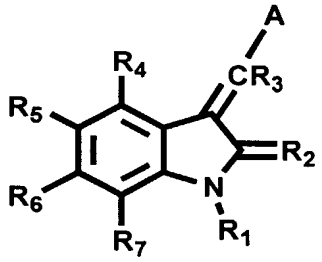
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R^{20} is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

[0122] A compound having the formula:



wherein:

R_1 is H;

R_2 is O or S;

R_3 is hydrogen;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, and CONRR';

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$ or CONRR';

n is 0-3;

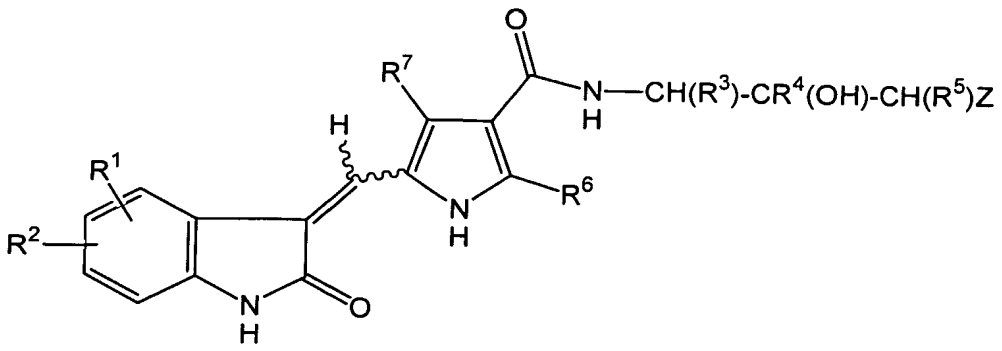
R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof.

[0123]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, $-C(O)R^8$, $-NR^9R^{10}$ and $-C(O)NR^{12}R^{13}$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)R^8$, $-S(O)_2NR^9R^{10}$ and $-SO_2R^{14}$ (wherein R^{14} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^3, R^4 and R^5 are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently hydrogen or alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are attached from a heterocycloamino group;

R^6 is selected from the group consisting of hydrogen or alkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and $-C(O)R^{17}$ as defined below;

R^8 is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

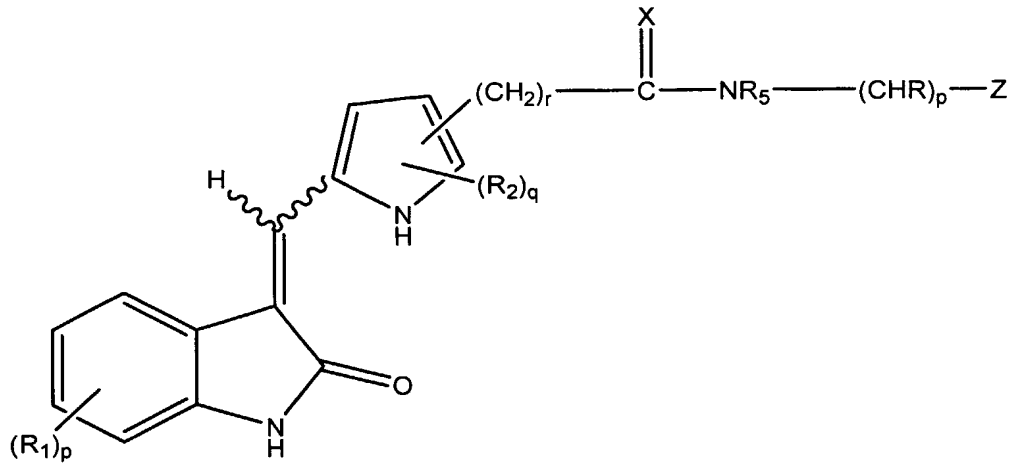
R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

[0124] In other embodiments of the invention, a mammal is exposed to a compound of Formula I:



(I),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8, -NR_9R_{10}, -$NR_9C(O)$-R_{12} and –$C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, –C(O)-R_8, and SO_2R'', where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8 and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

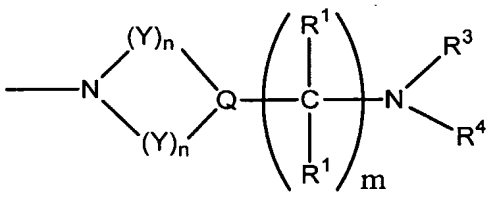
R_8 is selected from the group consisting of –OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of –OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2, N, O and S or



wherein Y is independently CH_2, O, N or S,

Q is C or N;

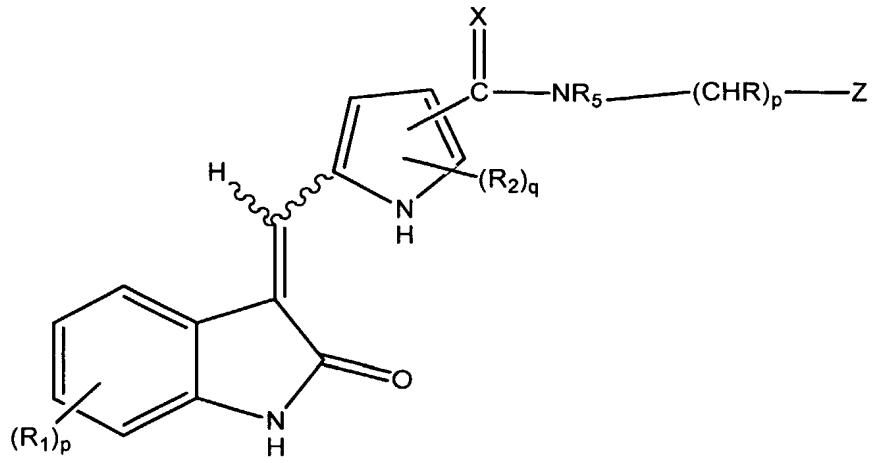
n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

[0125]

In another embodiment, a mammal is exposed to a compound of Formula II:



(II),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8, -NR_9R_{10}, -$NR_9C(O)$-R_{12} and –$C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, –C(O)-R_8, and SO_2R'', where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8 and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

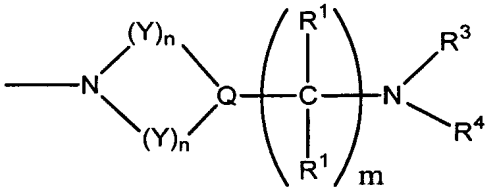
R_8 is selected from the group consisting of –OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of –OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2, N, O and S or



wherein Y is independently CH_2, O, N or S,

Q is C or N;

n is independently 0-4; and

m is 0-3;

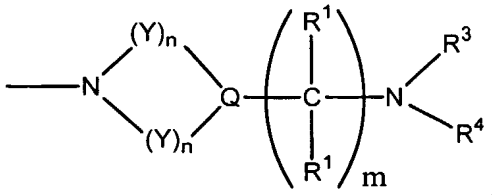
or a pharmaceutically acceptable salt thereof.

[0126] In another embodiment of the invention, a mammal is exposed to a compound of Formula I or II, wherein R_1 is halo (e.g., F and Cl) and Z is $-NR_3R_4$ wherein R_3 and R_4 are independently H or alkyl.

[0127] In another embodiment, Z of Formula I or II is $-NR_3R_4$, wherein R_3 and R_4 form a morpholine ring.

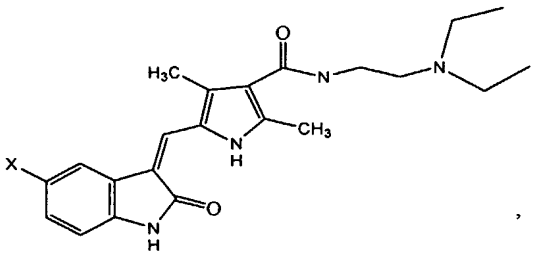
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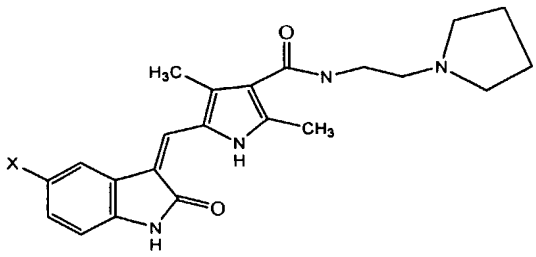
In another embodiment, Z of Formula I or II is:

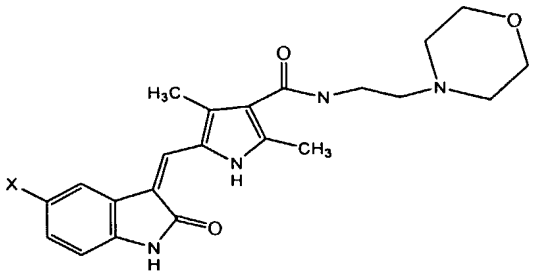


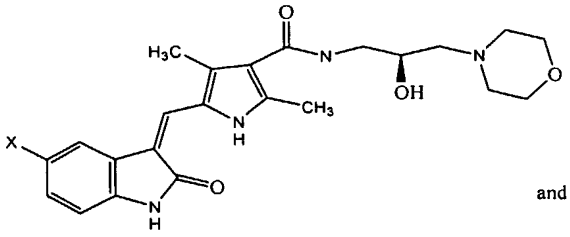
wherein each Y is CH_2, each n is 2, m is 0 and R_3 and R_4 form a morpholine ring.

[0129] In another embodiment of the invention, a mammal is exposed to a compound selected from the group consisting of

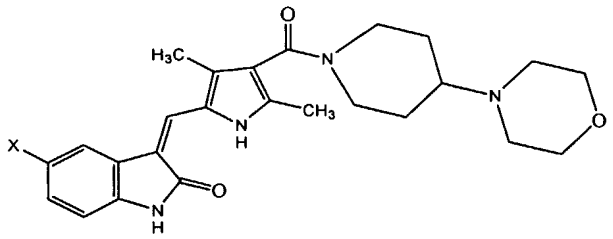








and



wherein X is F, Cl, I or Br; or a pharmaceutically acceptable salt thereof. In another embodiment, X is F.

[0130] In another embodiment of the invention, a mammal is exposed to a compound of Formula I selected from the group consisting of:

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound 2);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (Compound 3);

(S)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 4);

(R)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 5);

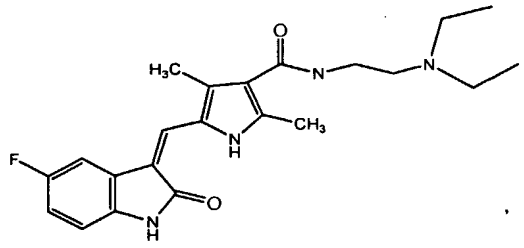
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 6);

5-(5-Chloro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 7);

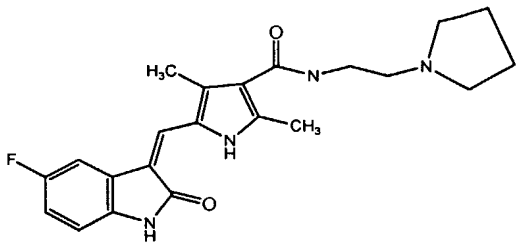
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethylamino-ethyl)-amide (Compound 8);

3-[3,5-dimethyl-4-(4-morpholin-4-yl-piperidine-1-carbonyl)-1H-pyrrol-2-methylene]-5-fluoro-1,3-dihydro-indol-2-one (Compound 9).

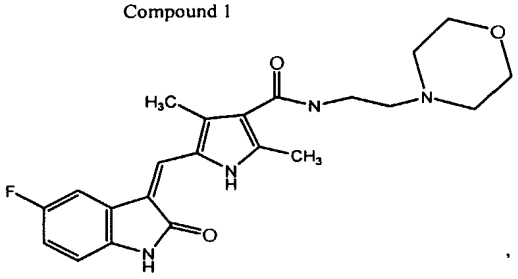
[0131] The above compounds are shown below:



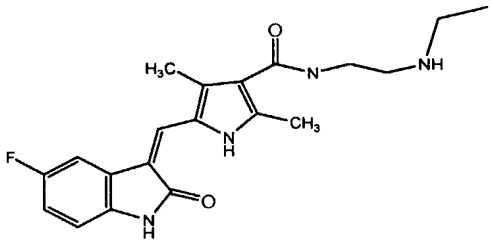
Compound 1



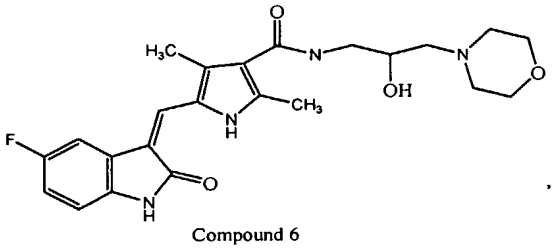
Compound 2



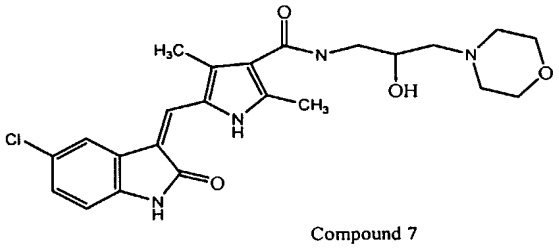
Compound 3



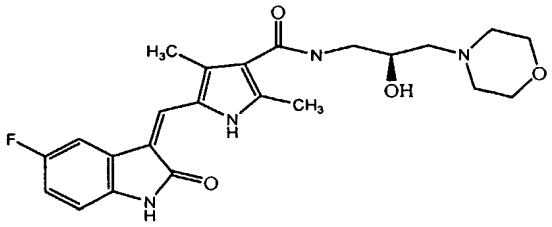
Compound 8



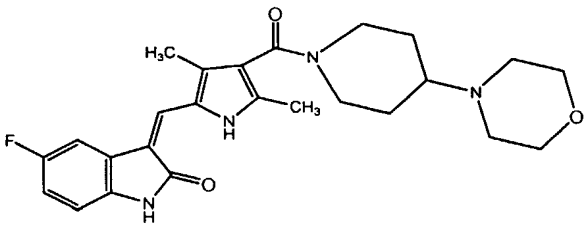
Compound 6



Compound 7

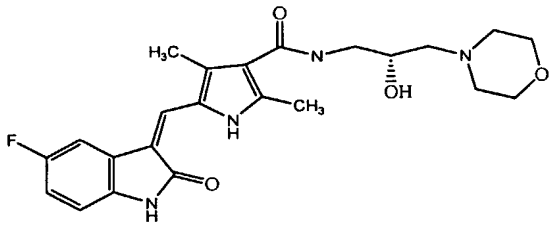


Compound 4



Compound 9

and



Compound 5

[0132] To clearly set forth the compounds of Formula I, Formula II and other compounds of the formulas described herein, useful in the inventive method, the following definitions are provided.

[0133] "Alkyl" refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 20 carbon atoms (whenever a numerical range; e.g. "1-20", is stated herein, it means that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). Alkyl groups containing from 1 to 4 carbon atoms are referred to as lower alkyl groups. When said lower alkyl groups lack substituents, they are referred to as unsubstituted lower alkyl groups. More preferably, an alkyl group is a medium size alkyl having 1 to 10 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, or tert-butyl, and the like. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more preferably one to three, even more preferably one or two substituent(s) independently selected from the group consisting of halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo , hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, $RS(O)_2$-, -C(O)OR,

RC(O)O-, and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, cycloalkyl, heterocyclic and aryl optionally substituted with one or more, groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups.

[0134] Preferably, the alkyl group is substituted with one or two substituents independently selected from the group consisting of hydroxy, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, or $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from the group consisting of hydrogen and alkyl. Even more preferably the alkyl group is substituted with one or two substituents which are independently of each other hydroxy, dimethylamino, ethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, morpholino, piperazino, 4-lower alkylpiperazino, phenyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolyl, triazinyl, and the like.

[0135] "Cycloalkyl" refers to a 3 to 8 member all-carbon monocyclic ring, an all-carbon 5-member/6-member or 6-member/6-member fused bicyclic ring or a multicyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with each other ring in the system) group wherein one or more of the rings may contain one or more double bonds but none of the rings has a completely conjugated pi-electron system.

[0136] Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, adamantane, cycloheptane, cycloheptatriene, and the like. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more

preferably one or two substituents, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen atoms of the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitogen (if present)atoms in the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto,(unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, $RS(O)_2$-, -C(O)OR, RC(O)O-, and $-NR_{13}R_{14}$ are as defined above.

[0137] "Alkenyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

[0138] "Alkynyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like.

[0139] "Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 1 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted.

When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, $RS(O)_2$-, -C(O)OR, RC(O)O-, and $-NR_{13}R_{14}$, with R_{13} and R_{14} as defined above. Preferably, the aryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0140] "Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two, or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, $RS(O)_2$-, -C(O)OR, RC(O)O-, and $-NR_{13}R_{14}$, with R_{13} and R_{14} as defined above. Preferably, the heteroaryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0141] "Heterocyclic" refers to a monocyclic or fused ring group having in the ring(s) of 5 to 9 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)n (where n is an integer from 0 to 2), the remaining ring atoms being C. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heterocyclic groups are pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, homopiperazino, and the like. The heterocyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted

lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, $RS(O)_2$-, -C(O)OR, RC(O)O-, and $-NR_{13}R_{14}$, with R_{13} and R_{14} as defined above. Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0142] Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0143] "Hydroxy" refers to an -OH group.

[0144] "Alkoxy" refers to both an -O-(unsubstituted alkyl) and an -O-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

[0145] "Aryloxy" refers to both an -O-aryl and an -O-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenoxy, pyridinyloxy, furanyloxy, thienyloxy, pyrimidinyloxy, pyrazinyloxy, and the like, and derivatives thereof.

[0146] "Mercapto" refers to an -SH group.

[0147] "Alkylthio" refers to both an -S-(unsubstituted alkyl) and an -S-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methylthio, ethylthio, propylthio, butylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, and the like.

[0148] "Arylthio" refers to both an -S-aryl and an -S-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenylthio, pyridinylthio, furanylthio, thientylthio, pyrimidinylthio, and the like and derivatives thereof.

[0149] "Acyl" refers to a -C(O)-R" group, where R" is selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted cycloalkyl, aryl optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihalomethyl, unsubstituted lower alkoxy, halo and $-NR_{13}R_{14}$ groups, heteroaryl (bonded through a ring carbon) optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and $-NR_{13}R_{14}$ groups and heterocyclic (bonded through a ring carbon)

optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and
$-NR_{13}R_{14}$ groups. Representative acyl groups include, but are not limited to, acetyl, trifluoroacetyl, benzoyl, and the like.

[0150] "Aldehyde" refers to an acyl group in which R" is hydrogen.

[0151] "Thioacyl" refers to a -C(S)-R" group, with R" as defined herein.

[0152] "Ester" refers to a -C(O)O-R" group with R" as defined herein except that R" cannot be hydrogen.

[0153] "Acetyl" group refers to a $-C(O)CH_3$ group.

[0154] "Halo" group refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

[0155] "Trihalomethyl" group refers to a $-CX_3$ group wherein X is a halo group as defined herein.

[0156] "Methylenedioxy" refers to a $-OCH_2O-$ group where the two oxygen atoms are bonded to adjacent carbon atoms.

[0157] "Ethylenedioxy" group refers to a $-OCH_2CH_2O-$ where the two oxygen atoms are bonded to adjacent carbon atoms.

[0158] "S-sulfonamido" refers to a $-S(O)_2NR_{13}R_{14}$ group, with R_{13} and R_{14} as defined herein.

[0159] "N-sulfonamido" refers to a $-NR_{13}S(O)_2R$ group, with R_{13} and R as defined herein.

[0160] "O-carbamyl" group refers to a $-OC(O)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0161] "N-carbamyl" refers to an $ROC(O)NR_{14}-$ group, with R and R_{14} as defined herein.

[0162] "O-thiocarbamyl" refers to a $-OC(S)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0163] "N-thiocarbamyl" refers to a $ROC(S)NR_{14}-$ group, with R and R_{14} as defined herein.

[0164] "Amino" refers to an $-NR_{13}R_{14}$ group, wherein R_{13} and R_{14} are both hydrogen.

[0165] "C-amido" refers to a $-C(O)NR_{13}R_{14}$ group with R_{13} and R_{14} as defined herein.

[0166] "N-amido" refers to a $RC(O)NR_{14}$- group, with R and R_{14} as defined herein.

[0167] "Nitro" refers to a $-NO_2$ group.

[0168] "Haloalkyl" means an unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above that is substituted with one or more same or different halo atoms, e.g., $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like.

[0169] "Aralkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with an aryl group as defined above, e.g., $-CH_2$phenyl, $-(CH_2)_2$phenyl, $-(CH_2)_3$phenyl, $CH_3CH(CH_3)CH_2$phenyl, and the like and derivatives thereof.

[0170] "Heteroaralkyl" group means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with a heteroaryl group, e.g., $-CH_2$pyridinyl, $-(CH_2)_2$pyrimidinyl, $-(CH_2)_3$imidazolyl, and the like, and derivatives thereof.

[0171] "Monoalkylamino" means a radical –NHR' where R' is an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., methylamino, (1-methylethyl)amino, cyclohexylamino, and the like.

[0172] "Dialkylamino" means a radical –NR'R' where each R' is independently an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., dimethylamino, diethylamino, (1-methylethyl)-ethylamino, cyclohexylmethylamino, cyclopentylmethylamino, and the like.

[0173] "Cyanoalkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above, which is substituted with 1 or 2 cyano groups.

[0174] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycle group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

[0175] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0176] As used herein, a "physiologically/pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

[0177] An "pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0178] As used herein, the term "salt" of a compound of Formula I, II or other formulas or compounds described in this specification refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(i) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylaminoethyl)amide; or

(ii) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0179] "Method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

[0180] "In vivo" refers to procedures performed within a living organism such as, without limitation, a mouse, rat or rabbit.

[0181] "Treat", "treating" and "treatment" refer to a method of alleviating, ameliorating, abrogating or relieving a disease condition and/or any of its attendant symptoms.

[0182] "Patient" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

[0183] "Therapeutically effective amount" refers to that amount of the compound being administered which will prevent, alleviate, ameliorate or relieve to some extent, one or more of the signs or symptoms of the disorder being treated.

ADMINISTRATION AND PHARMACEUTICAL COMPOSITION

[0184] In another embodiment of the invention, a human patient is exposed or administered a compound of Formula I, Formula II or other formulas or compounds described in this application, or a pharmaceutically acceptable salt thereof. Alternatively, the compounds of Formula I, Formula II or other formulas or compounds described herein can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, PA., latest edition.

[0185] As used herein, "exposing," "administer" or "administration" refers to the delivery of a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof of this invention to a mammal.

[0186] Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. The preferred routes of administration are oral and parenteral.

[0187] Furthermore, one administer the compound in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor progenitor.

[0188] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0189] Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0190] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0191] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl- pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0192] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0193] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also.

[0194] Pharmaceutical compositions which may also be used include hard gelatin capsules. As a non-limiting example, compound 1 in a capsule oral drug product formulation may be as 50 and 200 mg dose strengths. The two dose strengths are made from the same granules by filling into different size hard gelatin capsules, size 3 for the 50 mg capsule and size 0 for the 200 mg capsule.

[0195] The capsules may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation must be stored at controlled room temperature (15-30°C).

[0196] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0197] The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0198] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection

suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0199] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

[0200] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[0201] In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

[0202] A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

[0203] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

[0204] Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0205] The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0206]

Examples of formulations for use in the present invention are in Tables A-C:

TABLE A

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide hard gelatin capsules				
Ingredient Name	**Concentration in Granulation (% w/w)**	**Amount in 50 mg Capsule (mg)**	**Amount in 75 mg Capsule (mg)**	**Amount in 200 mg Capsule (mg)**
API	**65.0**	**50.0**	**75.0**	**200.0**
Mannitol	**23.5**	**18.1**	**27.2**	**72.4**
Croscaramellose Sodium[e]	**6.0**	**4.6**	**6.9**	**18.4**
Povidone (K-25)	**5.0**	**3.8**	**5.7**	**15.2**
Magnesium Stearate	**0.5**	**0.38**	**0.57**	**1.52**
Capsule	**-**	**Size 1**	**Size 3**	**Size 0**

TABLE B

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules		
Ingredient Name/Grade	**Concentration in Granulation (% w/w)**	**Amount in 50 mg Capsule (mg)**
API	**75.0**	**66.800[c]**
Mannitol	**13.5**	**12.024**
Croscaramellose Sodium[e]	**6.0**	**5.344**
Povidone (K-25)	**5.0**	**4.453**
Magnesium Stearate	**0.5**	**1.445**
Capsule	**-**	**Size 3**

TABLE C

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules				
Ingredient Name/Grade	**Concentration in Granulation (% w/w)**	**Amount in 25 mg Capsule (mg)**	**Amount in 50 mg Capsule (mg)**	**Amount in 100 mg Capsule (mg)**
API[a]	**40.0**	**33.400[d]**	**66.800[c]**	**200.0[b]**
Mannitol	**47.5**	**39.663**	**79.326**	**158.652**
Croscaramellose Sodium[e]	**6.0**	**5.010**	**10.020**	**20.04**
Povidone (K-25)	**5.0**	**4.175**	**8.350**	**16.700**
Magnesium Stearate	**1.5**	**1.252**	**2.504**	**5.008**
Capsule	**-**	**Size 3**	**Size 1**	**Size 0**

[a] Drug substance quantity required for the batch will be adjusted to have 100% of labeled strength for capsules. Appropriate adjustment will be made to mannitol quantity to keep the same fill weight for each strength.
[b] Quantity equivalent to 100 mg free base.
[c] Quantity equivalent to 50 mg free base.
[d] Quantity equivalent to 25 mg free base.
[e] Half intragranular half extragranular.

which can be found in U.S. Patent Application Serial No. 10/237,966, filed September 10, 2002, now a provisional application, which is expressly incorporated in its entirety by reference.

[0207] Many of the compounds of Formula I, Formula II or other formulas or compounds described herein may be provided as physiologically acceptable salts wherein the compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium, salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide ($Ca(OH)_2$), etc.).

[0208] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.,* a therapeutically effective amount.

[0209] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0210] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of phosphorylation of CSF1R). Such information can then be used to more accurately determine useful doses in humans.

[0211] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the IC_{50} and the LD_{50}, wherein the LD_{50} is the concentration of test compound which achieves a half-maximal inhibition of lethality, for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0212] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from in vitro data, e.g., the concentration necessary to achieve 50-90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[0213] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0214] At present, the therapeutically effective amounts of compounds of Formula I, Formula II or other formulas or compounds described in this application may range from approximately 25 mg/m^2 to 1500 mg/m^2 per day; alternatively about approximately 25 mg/m^2 to 1000 mg/m^2 per day. In another embodiment, the therapeutically effective amounts may range from approximately 25 mg/m^2 to 400 mg/m^2 per day.

[0215] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

[0216] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[0217] It is contemplated that the inventive method could be used in combination with other therapies, including chemotherapies, radiation therapies and surgical therapies for cancer. For combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the other agent can be determined by those of ordinary skill in the art, based on the effective amounts for the compounds described herein and those known or described for the other agent. The formulations and route of administration for such therapies and composition can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic and other agent in combination therewith.

[0218] Although all biomarkers disclosed in this specification are identified by specific sequences (and corresponding SEQ ID NOs), those skilled in the art will recognize that variants and alleles of these sequences also may function as biomarkers. Specific sequences, GenBank accession numbers and SEQ ID NOs in the specification are used to identify exemplary cDNAs, mRNAs and/or proteins of interest, and do not limit the invention to only those particular sequences. The biomarkers of the invention encompass variants and alleles of the disclosed sequences.

D. EXAMPLES – STUDIES USING COMPOUND A (SU6668)

1. Studies using Compound A – Materials and Methods

ELISAs

[0219] Reagents for human tissue inhibitor of metalloproteinase 1 (TIMP-1), human active and pro-matrix metalloproteinase 9 (total MMP-9) and human vascular endothelial growth factor (VEGF) ELISA kits were obtained from R& D Systems, Inc. (Minneapolis, MN). Human plasminogen activator inhibitor-1 (PAI-1) and human tissue factor (TF) ELISA kits were obtained from American Diagnostica, Inc. (Greenwich, CT). All ELISAs were performed on plasma samples according to the manufacturers' instructions.

2D gel analysis

[0220] Patient plasma was analyzed by 2D gel electrophoresis by Kendrick Labs (Madison, WI) according to the method of O'Farrell (J. Biol. Chem. 250: 4007-4021, 1975). Briefly, 150 ug of plasma protein was separated by isoelectric focusing using pH 4-8 gradient IEF gels. A 10% SDS/PAGE gel was used for the second gel dimension. Limited computerized comparisons were carried out on duplicate silver-stained gels and the spot percentage was calculated according to the formula: Difference = (1-spot % sample x/spot % sample ref)(-100). Spots whose abundance appeared to differ after Compound A exposure were subsequently excised and MALDI-TOF analysis was carried out for identification purposes.

Isolation of RNA from whole frozen blood

[0221] TRI Reagent®BD – RNA, DNA, protein isolation reagent was used according to the manufacturer's protocol, Molecular Research Center, Inc. (Cincinnati, OH) <www.mrcgene.com>.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0222] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/

expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total blood RNA (8 μg) of patient samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-$(dT)_{24}$ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for in vitro transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station. Images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0223] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1000 for these experiments). For comparisons between time points from a single patient, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the post-treatment sample was divided by the AD of the pre-dose samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 1.7 (increasing or decreasing).

TaqMan (qRT-PCR)

[0224] Primers and probes were designed using Primer Express 2.0 software, and purchased from Applied Biosystems (Foster City, CA). In all cases, primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). All probes contained a reporter dye (FAM) and a dye quencher (MGB). qRT-PCR was performed using 20 ng of total RNA with TaqMan® One-Step RT-

PCR Master Mix Reagents Kit (Applied Biosystems) following the manufacturer's protocol. The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. VEGF (Genbank accession number AF022375) transcripts were amplified using forward primer GCTCTCTTATTTGTACCGGTTTTTG (SEQ ID NO: 165), reverse primer AAGCTAGTGACTGTCACCGATCAG (SEQ ID NO: 166), and probe TCATGTTTCCAATCTC (SEQ ID NO: 167) to generate an 82-bp amplicon product. Vinculin (Genbank accession number M33308) transcripts were amplified using forward primer CCTGATATAAATGCAATATTAATGCCTTTA (SEQ ID NO: 168), reverse primer AAGAACCGGGAGAGCAAACAT (SEQ ID NO: 169), and probe ATCTATGCCAAAGATCACTT (SEQ ID NO: 170) to generate a 124-bp amplicon product. PECAM-1 (Genbank accession number L34657) transcripts were amplified using forward primer GGAGCACCGCCTGTGAA (SEQ ID NO: 171), reverse primer TGTGCGTTGCCTGAATGAAC (SEQ ID NO: 172), and probe ACCAACCTGAAGACAC (SEQ ID NO: 173) to generate a 56-bp amplicon product. MAPK Kinase 3 (Genbank accession number L36719) transcripts were amplified using forward primer TCTCGACTGAATGGACTTTGCA (SEQ ID NO: 174), reverse primer TTGTGTACCCCGCACCAA (SEQ ID NO: 175), and probe CACACCTCTATCCCGGC (SEQ ID NO: 176) to generate a 77-bp amplicon product. Hemoglobin, epsilon 1 (Genbank accession number AI349593) transcripts were amplified using forward primer GCTGCATGTGGATCCTGAGA (SEQ ID NO: 177), reverse primer TGAGTAGCCAGAATAATCACCATCA (SEQ ID NO: 178), and probe CTTCAAGCTCCTGGGTAA (SEQ ID NO: 179) to generate a 66-bp amplicon product. GAPDH and 18S were ordered as pre-developed assay reagents (PDARs) from Applied Biosystems and used as endogenous controls.

[0225] Data analysis of TaqMan (qRT-PCR): The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct scores for genes of interest for each sample were normalized against Ct scores for the corresponding endogenous control gene (GAPDH or 18S). Relative expression of specific transcripts in the post-dose sample compared to pre-dose sample was determined by the

following calculation, as described in the Applied Biosytems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} - 2^{-\Delta\Delta Ct},$$

Where $\Delta\Delta Ct = (Ct_{\text{target}} - Ct_{\text{control}})_{\text{post-dose}} - (Ct_{\text{target}} - Ct_{\text{control}})_{\text{pre-dose}}$.

2. Studies using Compound A – Results

ELISAs

[0226] Samples of plasma from human patients were taken before and 24 hours after the first dose of Compound A (SU6668). The patients were dosed twice over 24 hours with Compound A. The results of the ELISA analysis are shown in Figure 1, which shows that the levels of PAI-1, VEGF and TIMP-1 were increased in the plasma from patients exposed to Compound A. These proteins were therefore identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A. These patients were suffering from various types of cancer.

Two Dimensional Polyacrylamide Gel Electrophoresis

[0227] Samples of plasma from human patients suffering from advanced solid malignancies were taken before and 4 hours ater the first (and only) does of Compound A. A variety of proteins were increased and/or decreased in the plasma of patients treated with Compound A. As shown in Figures 2 and 3, mass spectrometry analysis identified one of these proteins (spot # 5) as ITIH4 (inter alpha (globulin) inhibitor H4). ITIH4 was therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A. *See* Figure 12 for sequences for ITIH4.

Microarrays and RT-PCR Analysis

[0228] Samples of whole blood from human patients suffering from advanced solid malignancies were taken before and 24 hours after the first dose of Compound A. An Affymetrix GeneChip analysis of the RNA transcripts present in patient blood before and after exposure to Compound A indicated that the levels of vinculin and VEGF RNA increase after exposure to Compound A (see Figure 4A and 4B). Vinculin and VEGF were therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A.

Microarrays and RT-PCR Analysis

[0229] Samples of whole blood from human patients were taken before and 27 days after the first dose of Compound A (in other words, samples were taken on day 0 and day 28; patients were dosed about 2 times per day on day 1-day 27, and following the first dose on day 28, the sample of blood was taken to measure biomarker(s). An Affymetrix GeneChip analysis of the RNA transcripts present in patient plasma before and after exposure to Compound A indicated that the levels of 26 transcripts were increased and/or decreased after exposure to Compound A (see Figure 5). Thus, 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A: eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792), Homo sapiens thymosin beta-10, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC call II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophillin, Genbank Accession No. AI541256 (cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, human KIAA0195, Homo sapiens MAP kinase kinase 3 (MKK3), human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA). *See* Figure 12 for sequences for these biomarkers.

E. EXAMPLES – STUDIES USING COMPOUND B (SU5416)

1. Studies using Compound B – Materials and Methods

Study Population

[0230] Patient samples were derived from 2 randomized, open-label, multicenter Phase III clinical trials comparing standard of care chemotherapy alone or combined with Compound B in patients with metastatic colorectal cancer. In both trials Compound B was delivered twice weekly at a dose of 145 mg/m^2 via I.V. infusion. In the first trial (designated Trial A), the standard of care chemotherapy consisted of weekly administration of 5-FU and leucovorin (Rosewell Park regimen); in the second trial (designated Trial B), the standard of care chemotherapy consisted of weekly or bi-weekly administration of 5-FU, leucovorin and

Irinotecan (CPT-11). A total of 23 patient sample pairs were included in Affymetrix microarray expression profiling analysis, 2 females and 9 males in the Compound B treatment arm, and 2 females and 10 males in the control arm. The median patient age was 66 and 65 years for the Compound B treatment arm and control arm, respectively. For RT-verification experiments, samples from 12 females and 24 males from the Compound B treatment arm, and 14 females and 17 males from the control arm were used. The median age for these patients was 62 and 60 years, respectively. Clinical response criteria were defined according to RECIST guidelines. Briefly, complete response (CR) is defined as complete disappearance of all measurable and evaluable clinical evidence of cancer; partial response (PR) is defined as at least a 50% reduction in the size of all measurable tumor areas; progressive disease (PD) is defined as an increase of ≥25% (compared to baseline or best response) in the size of all measurable tumor areas; and stable disease (SD) is defined as neither sufficient shrinkage to quantify for PR nor sufficient increase to qualify for PD.

Patient samples

[0231] All clinical samples for biomarker analysis were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the study informed consent prior to any study related procedures. All blood samples were collected into Vacutainer tubes containing sodium heparin. Ten 10 ml of blood was withdrawn from patients prior to receiving any treatment on day 1 and also prior to dosing at end of cycle 1 (day 56 in Trial A; day 42 in Trial B). For peripheral blood mononuclear cell (PBMC) preparations, blood samples were shipped overnight at ambient temperature to a central processing facility (Quest Diagnostics, Inc., Collegeville, PA, USA) for PBMC isolation via Ficoll gradient method. Purified PBMCs were shipped in RNA lysis buffer (Clontech, Palo Alto, CA, USA) to SUGEN where isolation of total RNA was performed. For Trial B, whole peripheral blood samples were directly frozen at the clinical sites and shipped on dry ice to SUGEN for RNA isolation.

RNA sample processing

[0232] Total RNA was purified from PBMC samples using Clontech Nucleospin RNA II kit reagents (Clontech, Palo Alto, CA) and from whole blood samples using MRC

TRI Reagent BD (Molecular Research Center, Cincinnati, OH, USA), an adaptation of the Chomczynski single step method, according to the manufacturer's instructions. All sample preparations included a treatment with RNAse-free DNAse. RNA yields were measured by UV absorbance and RNA quality was assessed by agarose gel electrophoresis with ethidium bromide staining for visualization of ribosomal RNA band integrity.

Affymetrix high-density oligonucleotide microarray analysis of PBMC expression profiles

[0233] In general, the standard RNA processing and hybridization protocols as recommended by Affymetrix (Santa Clara, CA, USA) were followed in this study; these protocols are available in the Genechip® Expression Analysis Technical Manual (viewable at <www.affymetrix.com/ support/technical/manual/expression_manual.affx>. Yields of total RNA for PBMC samples were generally low and for the majority of patients it was not possible to use the standard amount of total RNA ($\geq$ 5 μg) as recommended in the standard protocol. Therefore a double linear amplification approach was used in the generation of cRNA for hybridization. In these experiments, equal amounts of starting material were used for pre- and post-treatment samples from each donor (typically 2 μg). Briefly, the protocol was as follows: double-stranded cDNA was synthesized from total RNA (2 μg), with Invitrogen Life Technologies SuperScript Choice system reagents (Invitrogen, Carlsbad, CA). The T7-$(dT)_{24}$ oligomer was used for priming first-strand cDNA synthesis. Double-stranded cDNA product was purified via phenol-chloroform extraction, then used as template in first round of in vitro transcription (IVT) of cRNA. The IVT reaction was performed with BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol but with substitution of non-biotinylated ribonucleotides for biotinylated ribonucleotides. The cRNA product was then purified with Qiagen spin column clean-up protocol and used as template in second round of cDNA synthesis. This second round of synthesis was similar to the first round except that random hexamers were used in priming of first-strand synthesis, with T7-$(dT)_{24}$ oligomer priming the second-strand. Purification of the cDNA was as in the first round. The second round of IVT of cRNA was as in the first round but with biotinylated ribonucleotides rather than non-biotinylated ribonucleotides. Purified cRNA was quantitated, chemically fragmented according to Affymetrix protocol, and then hybridized overnight on Human Genome U95A Arrays (which contain probe sets for the detection of approximately 12,600

transcripts). Hybridized arrays were washed and stained with phyoerythrin-conjugated strepavidin detection chemistry in an Affymetrix Fluidics station, then images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0234] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The key output from individual arrays are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays. Average Difference determination relies on difference between background-subtracted signal from perfect match (PM) oligos and corresponding mismatch control (MM) oligos within a probe set representing a given transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a Scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (which was set at 1500 for these experiments). For comparisons between time points from a single patient, batch files were generated with Microarray Suite. These files contain calculated fold change (FC) values, which represent differential expression ratios of day 56 compared to baseline, and also Difference Calls (DC), which represent a more conservative estimate of differential expression, with qualitative scores assigned to each transcript measurement according to the following system: Increased (I), Marginally Increased (MI), No Change (NC), Marginally Decreased (MD), and Decreased (D).

[0235] Subsequent data analysis was performed primarily with Spotfire DecisionSite for Functional Genomics software (version 7) package and its Array Explorer component (Spotfire, Somerville, MA). Hierarchical clustering analysis and statistical comparisons were included in this step. Further refinement of the data, including filtering by Difference Call scores, was done with the Microsoft Access 97 database analysis program.

SYBR Green quantitative RT-PCR verification of array results

[0236] Primers were designed with Primer Express 1.5 software (Applied Biosystems). In all cases, primers were designed to bind within the sequence that was used in Affymetrix probe set designs (target sequence information available on Affymterix NetAffx website). Total RNA samples (1 μg) were reverse transcribed to yield first-strand cDNA using the Applied Biosystems Reverse Transcription Reagents protocol (Applied Biosystems, Foster City, CA). The reverse transcription reactions were then diluted 1:5 in distilled H_20.

SYBR Green PCR reactions were performed in 96-well optical plates and run in an ABI PRISM® 7700 Sequence Detection System (SDS) machine. For individual reactions, 10 µl of each sample were combined with 15 µl of SYBR Green PCR Master Mix (Applied Biosystems) containing the appropriate primer pair at 350 nM. Data was extracted and amplification plots generated with ABI SDS software. All amplifications were done in duplicate and threshold cycle (C_t) scores were averaged for subsequent calculations of relative expression values. The C_t scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. Heat dissociation curve analysis was performed after each SYBR Green run as a test of whether a single product had been generated in each PCR reaction; multiple peaks in the dissociation curves are indicative of multiple PCR products and thus reduced specificity and sensitivity.

Quantitation and statistical analysis of SYBR Green PCR data

[0237] The C_t scores for genes of interest for each sample were normalized against C_t scores for the corresponding endogenous control gene, which was the β-glucoronidase (GUS) gene in these experiments. Relative expression for day 56 compared to day 1 was determined by the following calculation, as described in the Applied Biosytems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} - 2^{-\Delta\Delta Ct},$$

Where $\Delta\Delta Ct = (Ct_{\text{Target}} - Ct_{\text{GUS}})_{\text{day 56}} - (Ct_{\text{Target}} - Ct_{\text{GUS}})_{\text{day 1}}$.

[0238] The relative expression data for a select subset of potential biomarkers were tested for differences between the Compound B (treatment) and the standard of care (control) arms. The Mann-Whitney U Test with a critical alpha level of 0.05 was used for statistical significance. Individual genes observed to be significantly different by Affymetrix analysis and in both sets of SYBR Green RT-PCR experiments were screened as potential biomarker candidates. This subset of potential biomarker candidates was tested subsequently for utility as class predictors to discriminate between the Compound B and standard of care arms. Discriminant analysis, a multivariate statistical technique, was used for this purpose. The genes were tested individually, using all possible combinations, by reducing dimensions (Principal Component Analysis) in order to determine the subset of genes (predictor variables) that yielded highest classification accuracy. Cross-validation was used to test the robustness of classification accuracy. Results from three different cross-validations were evaluated to select the best set of predictable biomarkers: (1) jackknife method (dropping

one case at a time); (2) randomly splitting the pooled data into two halves, prediction (for building model) and validation (for testing model); and (3) using the first trial as prediction and the later trial as validation sets, respectively. All statistical analyses were carried out after natural-log transformation on the data; SYSTAT 9.01 (SPSS, Inc., Chicago, IL, USA) software was used in statistical analysis.

2. Studies using Compound B – Results

Affymetrix expression profiling of pre- and post-treatment matched PBMC samples

[0239] Expression profiling using Affymetrix high-density oligonucleotide microarrays was applied to PBMC samples harvested from patients in a Phase III clinical trial of Compound B in Trial A. The PBMC samples were harvested at baseline (day 1) and at end of cycle 1 (day 56) from patients receiving standard-of-care (5-FU/leucovorin) treatment and from those receiving standard-of-care plus Compound B. Sample pairs from 23 patients were processed and the dataset was filtered for expression changes that consistently correlated with the treatment arm (Compound B). Of 13 genes that met the initial requirement, 6 were further tested by quantitative RT-PCR analysis of additional patient samples from patients.

[0240] Table 1 includes a summary of the total samples processed. As RNA yields rarely exceeded 2 μg, a double amplification step was used in cRNA generation for the samples that were used (see Materials and Methods). Only samples from patients with cycle 1 responses of either PR/CR or PD were used in the final dataset.

[0241] Batch comparison files were generated for each day 1/day 56 sample pair after hybridization. Batch comparisons included both fold change (FC) values as calculated by Affymetrix Microarray Suite software as well as difference calls (DC). DC offer a more stringent but non-numerical measure of whether levels of a transcript are different in the 2 samples. Batch comparison results for the 23 cases were analyzed with Spotfire Decision Site software tools. Initial analysis suggested there was more similarity among patient samples of the same treatment arm than among samples of the same response category (PR/CR or PD) independent of treatment arm. Therefore, subsequent analysis focused on identification of transcripts that were differentially expressed in the Compound B arm but not in the control arm.

[0242] The Treatment Comparison tool in Spotfire was used to identify transcripts that were statistically significantly different in the two treatment arms; this tool uses t-test analysis of averaged fold changes for each group. To further refine this subset of genes, queries based on DC status were performed with Microsoft Access. The data were filtered to identify those genes that were called 'Increased' (I) or 'Decreased' (D) in a majority of the Compound B arm cases. A group of 13 genes that frequently showed increased expression was identified. Figure 6 displays a schema of the DC scores assigned to each gene for each patient sample pair. All cases from the Compound B arm show induction in at least 6 of the 13 genes.

[0243] Table 2 includes a brief summary of putative biological function for each of the 13 gene products, as well as an ID number assigned by Affymetrix to each transcript-specific probe. The last two columns in Table 2 list the number of patients in which transcript levels were increased at day 56 relative to day 1 (i.e., an 'Increase' call was assigned). Total number of patients is 11 for the Compound B (SU5416) arm and 12 for the control arm. The average fold change of all of these transcripts was higher in the Compound B (SU5416) arm (the lowest average fold change was 2.6 for hypothetical protein FLJ13052, the highest was 33 for lactoferrin); the range of fold changes was also broader in this category, presumably representing variability among patients.

Quantitative RT-PCR validation of differentially expressed transcripts

[0244] To validate the microarray results, a subset of these transcripts was chosen for quantitative RT-PCR analysis. Primer sets were designed for 6 of the 13 genes; matrix metalloproteinase-9 (MMP-9), thrombospondin-1 (TSP-1), CD24, defensin α 3, lipocalin 2 (LCN2), and lactoferrin. These 6 genes were chosen based on potential roles of encoded proteins (for example, thrombospondin-1 and MMP-9 have known roles in angiogenesis) or because of the degree to which they appeared to be differentially regulated between treatment arms. The lipocalin-2 gene (LCN2) has been reported to be inducible by dexamethasone (Science, 293: 829-34 (2001)). Dexamethasone is one of the premedications administered to patients in the Compound B arm. Table 3 describes the forward and reverse primers that were used in validation of these transcripts.

[0245] SYBR Green chemistry was used to validate the microarray expression profiling data. SYBR Green is a dye that fluoresces when bound to double-stranded DNA,

thus signal is directly proportional to the amount of product formed during PCR amplification. This method allows rapid and inexpensive comparison of gene expression across a large number of samples. The qRT-PCR validation was performed with a total of 31 Compound B patient sample pairs, 8 of which had previously been analyzed on Affymetrix U95A arrays and thus allowed a comparison of the correlation between the 2 transcript profiling methods. Of the 31 samples, 18 were from the Compound B arm and 13 were from the control arm.

[0246] Data for each gene was normalized to expression of a housekeeping gene, β-glucoronidase (GUS). By direct comparison of SYBR Green RT-PCR results and Affymetrix results from the same cases, the overall qualitative correlation (i.e., same trend of induction or no change detected in both samples) was greater than 70%. This number is perhaps an underestimate since results for one patient were completely discordant between methods and thus potentially due to experimental artifact.

[0247] Figure 7 summarizes the results from the RT-PCR validation and compares them with those from the Affymetrix analysis. It is clear that there are some differences in the trends displayed in the 2 datasets. This is further demonstrated by statistical analysis, as Mann-Whitney U test comparison of Compound B and control results from both analyses indicates that only 4 of the 6 genes display statistical significance (Table 4). These 4 genes are CD24, lactoferrin, LCN2, and MMP-9. (MMP-9 exhibited a p-value that was close to the significance cutoff and thus was also selected for further analysis.)

Qualitative RT-PCR validation of differentially expressed transcripts with samples from a second Phase III Compound B trial

[0248] To further confirm these transcripts as biomarkers of Compound B administration, SYBR Green RT-PCR analysis of these 4 transcripts was carried out in a collection of samples from a second Phase III trial (Trial B). In this randomized metastatic colorectal cancer study, 5-FU/leucovorin/CPT-11 was administered as the standard of care, and compared to the standard of care plus Compound B. RNA samples from patients in this trial were derived from frozen whole blood (rather than purified PBMCs), and harvested at the beginning (pre-dose day 1) and at the end (day 42) of cycle 1. To test if similar results occurred, analysis was performed on 36 sample pairs, 18 from Compound B arm and 18 from control arm. Due to limited numbers of available samples, many of the cases analyzed in this

analysis were from patients with stable disease (SD) at cycle 1 assessment rather than PR/CR and PD as in the previous approaches.

[0249] Figure 8 summarizes the overall behavior of the transcript levels in both trial arms in terms of the frequency with which the transcripts showed an induction (here defined as relative expression, day 42 vs day 1) of 2-fold or greater in each arm. It is clear that there is more induction of these transcripts at day 42 in the Compound B arm than in the control arm. This is also reflected in statistical analysis, as indicated in results of the Mann-Whitney U Test of this dataset (Table 5).

[0250] A visual representation of hierarchical clustering analysis of the qRT-PCR relative expression values from both trials for each of the transcripts is displayed in Figure 9. This clustering pattern displays the distinction between the Compound B and control arms based on relative expression data, and also indicates further distinctions among subsets of patients as well as the degree of overlap between trial arms in the clustering pattern. The extent of similarity between the relative expression patterns for each transcript (represented in columns) is also indicated; the pattern of MMP-9 is distinct from the others as it appears in a separate branch in the dendrogram structure.

Discriminant analysis of the classification power of biomarkers

[0251] We tested whether relative expression data from these samples could be used in a predictive fashion to classify samples to the appropriate trial arm. To test this, discriminant analysis of the SYBR Green RT-PCR data was performed. Relative expression values from both the first and the second dataset were combined, after comparison of mean relative expression ratios and standard deviations indicated greater similarity between respective trial arms rather than between control and Compound B arm in either trial alone. The relative expression ratios were then natural log-transformed to reduce the scale of the values and thus make control and treated arms more comparable. When the samples were pooled (67 cases altogether) and subjected to classification prediction, a total prediction accuracy of 84% was achieved. Further cross-validation was performed by the jack-knife method (which does a series of predictions, randomly removing 1 case from the total each time), and by splitting the data set into 2 random halves (one a 'training' set and the other a 'testing' set).

[0252] The results from each of these steps are summarized in Table 6 for a set of 3 of the 4 transcripts that gave the best accuracy percentage (including MMP-9 slightly reduced the accuracy of cross-validation). Thus, it is predicted that expression data from these 3 genes would accurately distinguish Compound B arm patients from control arm in between 67% to 84% of cases. When the first trial data was used as the 'training' set and the second trial data as the 'testing', as opposed to randomly selecting the data, the % accuracy in cross-validation was 86% and 77% for the training and testing set, respectively. Cross-validation results are displayed for two different approaches. In section 2 of Table 6, one case is dropped at a time and its group membership predicted from the other cases. In sections 3 and 4, cross-validation is carried out by using a randomly selected half of the cases as a training set and the remaining half as a test set. Section 4 summarizes the prediction accuracy achieved when the group in section 3 is used as a training set.

Conclusions: Compound B Studies

[0253] Large-scale gene expression analysis was applied to blood RNA samples from a clinical trial of Compound B to investigate changes in gene expression that might correlate with exposure to cancer therapy. Independent quantitative RT-PCR validation of initial array hybridization results was performed on larger sample populations from two conceptually similar Phase III clinical trials using Compound B. A set of 4 transcripts (CD24, lactoferrin, LCN2, and MMP-9) was identified whose expression was significantly induced at the end of one treatment cycle relative to baseline following Compound B administration. Discriminant analysis indicates that data derived from the RT-PCR study would have a class prediction accuracy of at least 70%.

[0254] These 4 transcripts are considered to be biomarkers of Compound B administration and other compounds that inhibit tyrosine kinase. These results also demonstrate that human blood samples can serve as surrogate tissues for biomarker investigations and that large-scale gene expression analysis is a useful approach for characterization of clinical trial samples.

F. EXAMPLES – FURTHER STUDIES USING COMPOUND B (SU5416)

Baseline and post-treatment levels of PAI-1 in Compound B patient plasma

[0255] PAI-1 plasma levels were examined in samples from Compound B patients. Interestingly, median PAI-1 levels decreased after 56 days of treatment in samples from all patients examined with a MR (minor response) at the end of cycle 1 (Figure 10, n = 37; Compound B arm day 1 median 40.66 ng/ml, day 56 median 23.93 ng/ml, 5FU/LV arm day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml). In contrast, median PAI-1 levels in samples from all patients examined with a PD (progressive disease) response at the end of cycle 1 did not appear to change significantly (Figure 10, n = 47; Compound B arm day 1 median 26.47 ng/ml, day 56 median 34.8 ng/ml, 5FU/LV arm day 1 median 25.67 ng/ml, day 56 median 23.29 ng/ml). Furthermore, the decrease in PAI-1 plasma levels in the control arm MR patients after 56 days of treatment was statistically significant (day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml, P = 0.0003; n = 20). The decrease in PAI-1 levels of Compound B arm patients was not statistically significant (P = 0.095; n = 17). These data indicate that changes in plasma PAI-1 levels after one cycle of treatment correlate with cycle one clinical response of both the experimental and control arm regimens.

Pre-treatment levels of PAI-1

[0256] An analysis of the pre-treatment plasma levels of plasminogen activator inhibitor-1 (PAI-1) shows that pre-treatment levels also correlate with clinical response (on day 56) in either arm, indicating that PAI-1 is a biomarker predictive of response to tyrosine kinase inhibitor in advanced colorectal cancer.

[0257] An analysis of the pre-treatment levels of PAI-1 indicated that patients with an MR response (cycle 1) had a statistically significantly (P = 0.001) higher level of plasma PAI-1 (median 41 ng/ml; n = 37) than that of patients with a PD response (median 26 ng/ml; n = 47) regardless of the regimen subsequently received. Thus far, only 4 patients that had a partial response (PR) at the end of cycle 1 have been examined for PAI-1 plasma levels. These patients have pre-treatment levels (median 37.4 ng/ml) similar to the MR patients (median 40 ng/ml), however PAI-1 levels did not decrease significantly in these patients samples after 56 days of treatment. These results (see Figure 10) indicate that the pre-treatment levels of plasma PAI-1 are predictive of MR response (as compared to a PD response) to either the experimental or the control arm regimen.

[0258] The present invention includes a method for predicting the probability of whether a patient will respond positively to administration of a tyrosine kinase inhibitor, comprising measuring the level of PAI-1 in patient plasma, wherein a level of greater than 30 nanograms/per ml of plasma, or greater than at least 35 nanograms, or greater than at least 37 nanograms per ml, indicates a positive probability that the patient will respond positively to administration of a tyrosine kinase inhibitor.

G. EXAMPLES – STUDIES USING COMPOUND 1

1. Studies using Compound 1 – Materials and Methods

[0259] A panel of proteins were investigated for their utility as biomarkers of Compound 1 in cancer patients receiving the compound in Phase I trials. The patient samples were from a total of four Phase I trials, 3 of which were open to patients with any advanced solid malignancy (these were Trials A, B and C) and one of which (Trial D) was a trial in patients with Gleevec-refractory, resistant, or intolerant gastrointestinal stromal tumors (GIST). In all cases, plasma samples were available from just before first Compound 1, or malate salt thereof, dose (baseline) and at various time points during dosing. In Trials A and B, patients received Compound 1. In Trials C and D, patients received a malate salt of Compound 1. For methods of making Compound 1, *see* U.S. Ser. No. 09/783,264 or WO 01/60814, U.S. Ser. No. 10/076,140 or U.S. Ser. No. 10/281,985, the disclosures of which are incorporated by reference. For methods of formulating Compound 1, *see* U.S. Ser. No. 10/237,966 (now a U.S. provisional application), the disclosure of which is incorporated by reference.

[0260] All of the ELISA-based screening of candidate proteins were performed with commercially available ELISA kits; the kits for the biomarkers described in this report are all available from R&D Systems (Minneapolis, MN). A commercially available membrane array containing antibodies for the detection of 42 human cytokines was also used in screening of a patient's plasma samples before and after treatment. The antibody array used in cytokine screening (RayBio Human Cytokine Array III) was from RayBiotech (Norcross, GA).

[0261] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol. Study participants signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood

samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site. The time points for which plasma samples are available in each trial are as follows:

Trial A (4 weeks on/ 2 weeks off dosing schedule):
plasma – Day 1 (0, 6, 24 hr); Day 28 (0, 6, 24 hr)

Trial B (2 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6, 12, 24 hr); Day 13 (0, 6, 12, 24 hr)

Trial C (4 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6 hr); Day 15, 29, 42* (Cycle 1); Day 1, 15, 29 (Cycle 2)

Trial D (2 weeks on/ 2 weeks off):
Plasma – Day 1, 7, 14, 28* (Cycle 1); Day 1 only, in subsequent cycles

Trial E (4 weeks on/2 weeks off):
Plasma – Day 1, 3, 28 (Cycle 1)

* 'washout' sample

Plasma samples were also collected from a set of 10 SUGEN healthy donors; plasma was collected at 3 time points for each donor (day 1, 14, and 28) to mimic time points used in the Phase I trials and thus serve as controls for the normal level of fluctuation of plasma markers in the absence of Compound 1 treatment.

[0262] Data analysis was performed for each marker. This was done by generating ratios of plasma levels at various time points during treatment versus the plasma levels at baseline (pre-dose on day 1, cycle 1), or by comparing absolute plasma concentrations at times during treatment to the baseline absolute plasma concentrations. For correlative analysis, scatter plots were drawn and linear regressions were calculated comparing fold change (end of cycle 1 dosing to baseline) of each marker to corresponding values assigned to clinical parameters such as pharmacokinetics, drug dosage, and ^{18}FDG-PET functional imaging.

2. Studies using Compound 1 – Results

[0263] A panel of candidate proteins was evaluated by ELISA analysis in plasma samples from cancer patients receiving Compound 1 or malate salt thereof. Of those investigated, a subset was observed to change consistently in patients receiving Compound 1 or malate salt thereof. One of the proteins was Vascular Endothelial Growth Factor (VEGF);

large increases (greater than 3-fold) in plasma levels were seen in approximately 70% of patients in Trials A, B and C, and in a small proportion of patients in Trial D.

[0264] Figure 13 displays typical pattern of VEGF plasma levels seen in Trial C. VEGF levels are observed to rise by day 15 of cycle 1 and typically peak at day 29, then tend to subside to near baseline levels by day 42, which is the end of the 2-week drug rest period, or 'washout', in these patients.

[0265] To further investigate this, levels of a related angiogenic factor, Placenta Growth Factor (PLGF), were measured in some of the same patients as in the VEGF tests. As shown in Table 7, levels of PLGF are induced in a majority of patient samples that were tested, and follow a similar pattern as VEGF in that levels are most induced at day 29 and decline by day 42.

[0266] A further question regarding VEGF and PLGF was whether the presence of VEGF/PLGF heterodimers in patients' plasma could be detected, and whether levels of the heterodimer could be modulated by treatment with Compound 1 or malate salt thereof. Heterodimers of VEGF and PLGF have been reported in the scientific literature. To measure heterodimers, a hybrid ELISA assay was used, combining reagents from both the R&D Systems VEGF and PLGF ELISA kits (where VEGF antibodies are used in capture step and PLGF antibodies are used in detection step).

[0267] The results of applying this assay to plasma samples from 3 patients are shown in Figure 14. Data from the same samples for VEGF and PLGF are also shown in the graphs in Figure 14. A similar pattern of induction of the VEGF/PLGF heterodimer as was seen for VEGF and PLGF was observed. In 3 of 3 patients tested, an increase in plasma levels of VEGF/PLGF heterodimer is observed, indicating that both PLGF and the VEGF/PLGF heterodimer are novel biomarkers of Compound 1 activity in patients.

[0268] Another protein, VEGF receptor 2 (VEGFR2) was investigated. VEGFR2 is one of the targets of Compound 1 and is important in angiogenesis. Whether soluble VEGFR2 is detectable via ELISA in plasma samples from cancer patients was investigated, as well as whether levels of the protein would change in response to treatment with Compound 1 or malate salt thereof.

[0269] Intriguingly, levels of the plasma soluble form of VEGFR2 were observed to decrease in the vast majority of patients (greater than 90%) in Trials A, B and C at chronic time points (13 days or more) after the start of treatment with Compound 1 or malate salt

thereof. Also, in Trial D, a dose-dependency of the sVEGFR2 decrease was seen, as changes were clearly observed in a cohort of patients in that trial receiving 50 mg daily doses of a malate salt of Compound 1, but not observed in a cohort of patients receiving 25 mg daily doses (Figure 15). The difference between the dose cohorts was statistically significant as judged by t-test. Also, levels of sVEGFR2 typically increased to near baseline levels at the end of the 2-week drug rest period in patients from all 4 trials, thus exhibiting a pattern similar in timing but opposite in direction to that seen for VEGF and PLGF (Table 9). Table 9 displays results for sVEGFR2 in individual patients, and also includes results for PLGF where available. Also included in Table 9 is information on the types of cancers found in the patients.

[0270] Further, data suggests that there exists some correlation between the extent of decrease in plasma sVEGFR2 and pharmacokinetics measurements of drug exposure in patients. This is demonstrated in Figure 16, which shows a scatter graph plotting change in sVEGFR2 plasma level (ratio of level on last day of cycle 1 dosing to baseline level) against area under curve (AUC) drug exposure measurements (from last day of cycle 1 dosing). The graph is a composite of data from all 4 trials, and the R-squared value indicates there is some association between decrease in sVEGFR2 and drug exposure. Thus, soluble VEGFR2 is a novel marker of Compound 1 treatment and may be a marker of both drug exposure and biological activity of the compound.

[0271] Another potential biomarker of Compound 1 was identified first in an array-based screen of plasma samples, before and after Compound 1 treatment, from a patient in Trial B. The array screen utilized a commercially available antibody membrane array, which in principle allows for simultaneous measurement of 42 different human cytokines. Results of the screen indicated that levels of a protein called Monokine Induced by Interferon-gamma, or MIG, were significantly higher after treatment with Compound 1 than in baseline samples. This result was confirmed via an MIG ELISA assay on the same patient samples. Following confirmation, levels of MIG in plasma were assessed for a number of patients from Trial C. These results showed that MIG was induced more than 3-fold in 30-40% of the patients tested (data not shown).

[0272] There is evidence of a correlation between increased MIG levels and a positive response in the functional imaging assay of ^{18}FDG-PET (a feature of Trials C and D). This is illustrated in Figure 17; those patients with at least a mixed response based on PET imaging tended to have higher folds of induction of secreted MIG protein. To further

investigate the induction of MIG observed in patients, we have also measured the plasma levels of IP-10 and I-TAC before and after treatment with Compound 1 or malate salt thereof. IP-10 and I-TAC, like MIG, are regulated at the expression level by interferon-gamma, and both IP-10 and MIG have roles in chemoattraction of immune cells and exhibit angiostatic (anti-angiogenic) activity. Interestingly, evidence suggests that MIG and IP-10 are induced in tandem in 6 of 6 patients checked for both proteins while MIG and I-TAC are induced in tandem in 5 of 5 (Table 8). Similarly, all 3 proteins are induced in the 2 patients where all of the 3 were checked (Table 8). Table 10 indicates the types of cancer found in patients where MIG is induced. Thus, evidence indicates that MIG, IP-10 and I-TAC are novel biomarkers that are modulated in Compound 1 patients and are markers that correlate with an anti-tumor response as measured by PET imaging.

[0273] In summary, ELISA-based screening of plasma samples from Phase I clinical trials using Compound 1, or malate salt thereof, has yielded a set of circulating proteins that are novel surrogate markers for Compound 1 drug exposure and/or biological activity. Soluble VEGFR2 has been identified in plasma as a marker of drug exposure, while VEGF, PLGF, and VEGF/PLGF heterodimers have been frequently observed to increase in a majority of patients and appear to be correlates of biological activity and (to a lesser extent than sVEGFR2) drug exposure. MIG, IP-10 and I-TAC are additional biomarkers that appear to correlate with anti-tumor activity as measured by ^{18}FDG-PET functional imaging.

H. EXAMPLES – FURTHER STUDIES USING COMPOUND 1

1. Further studies using Compound 1 – Materials and Methods

***In Vivo* Animal Studies**

[0274] Female athymic-*nu/nu* mice (Charles River, Hollister, CA) were injected with Colo205 human colon cells ($5x10^6$ cells) subcutaneously. The animals were treated with a single dose of either citrate vehicle or Compound 1 at 40 mg/kg when the tumors are approximately 350-400 mm^3 in size. For biomarker studies, tumors were harvested at six and 24 hours post-treatment and snap frozen for RNA extraction.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0275] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, total RNA from tumor samples was prepared using Nucleospin RNA II Kit in accordance with the manufacturer's recommendation (Clontech, Palo Alto, CA). RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total RNA (8 μg) of tumor samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-$(dT)_{24}$ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for *in vitro* transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station.

Images were scanned with a Hewlett-Packard GeneArray scanner. All techniques were performed on xenograft tissue samples according to the manufacturers' instructions.

Data analysis of DNA microarray

[0276] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1500 for these experiments). For comparisons between different treatments from a single time point, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the drug-treated samples was divided by the AD of the vehicle-treated samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 2.0 (increasing or decreasing).

Taqman Real-Time RT-PCR Assay

[0277] Primers and probes were designed using Primer Express 2.0 software (Applied Biosystems, Foster City, CA). All primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). Taqman probes were labeled with reporter dye, 6-carboxy-fluorescein phosphoamidite (FAM), at the 5′ end and dye quencher, minor groove binder (MGB), at the 3′ end. Each 25-µl reaction consisted of 500 nm forward primer, 500 nm reverse primer, 100 nm of Taqman probe, cDNA (20 ng of total RNA from tumor samples), and 1X (final concentration) of Taqman® One-Step RT-PCR Master Mix Reagents Kit (Applied Biosystems). The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. 18S ribosomal gene's primers and probe pairs were purchased from Applied Biosystems and used according

to manufacturer's recommendation as an endogenous control. All techniques were performed on the tissue samples according to the manufacturers' instructions.

Data analysis of Taqman assay

[0278] The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct score for genes of interest for each sample were normalized against Ct score for the corresponding endogenous control gene (18S). Relative expression of specific transcripts in the drug-treated sample compared to vehicle-treated sample was determined by the following calculation, as described in the Applied Biosytems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Relative Expression} = 2^{-\Delta\Delta Ct},$$

where $\Delta\Delta Ct = (Ct_{\text{target}} - Ct_{\text{18s control}})_{\text{drug treatment}} - (Ct_{\text{target}} - Ct_{\text{18s control}})_{\text{vehicle treatment}}$.

2. Further Studies using Compound 1 – Results

Microarrays and RT-PCR Analysis

[0279] To identify biomarker(s), samples of tissue from the tumors were taken before and after the first dose of Compound 1. An Affymetrix GeneChip analysis of the RNA transcripts present in xenograft tissue before and after exposure to Compound 1 indicated that the levels of 28 transcripts increased and/or decreased after exposure to Compound 1 (see Table 11A and 11B). Thus, the following 26 proteins/trasnscripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound 1: basic transcription factor 3 homologue, human c-jun proto-oncogene, human c-fos proto-oncogen, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, vinculin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, gelsolin and cyclin D2. *See* Figure 24 for sequences for these biomarkers.

[0280] To validate the Affymetrix GeneChip results, a subset of 11 of these 26 transcripts was chosen for quantitative RT-PCR analysis. These 11 transcripts were chosen

based on potential roles of encoded proteins. Table 13 describes the forward and reverse primers that that were designed and used in the RT-PCR experiments. The results of the quantitative RT-PCR analysis for these 11 transcripts are shown in Table 12. The RT-PCR analysis confirms the findings with the Affymetrix GeneChip analysis for these 11 transcripts.

I. EXAMPLES – ADDITIONAL STUDIES USING COMPOUND 1

1. Additional studies using Compound 1 – Materials and Methods

Human Umbilical Vein Endothelial Cells (HUVECs)

[0281] HUVECs were obtained from Clonetics (San Diego, CA catalog# CC-2517) and were maintained in EGM media (Clonetics, catalog# CC-3121) containing EGM BulletKit (Clonetics, catalog# CC-4133: 2% Fetal Bovine Serum, 0.1% Epidermal Growth Factor, 0.1% Hydrocortisone, 0.1% Gentamicin Sulfate Amphotericin B, 0.4% Bovine Brain Extract). Cells were propagated at 37°C in a humidifed atmosphere of 5% CO_2 using standard cell culture techniques. Cells were plated in 10-cm tissue culture plates at 8.5 X 10^5 cells/ml. After 6 hours the cells were quiesced by serum starvation overnight in starvation medium (EBM containing 0.5% FBS). DMSO (Sigma Chemicals, St. Louis, MO #D2650) or Compound 1 (to a final concentration of 10 nM, 100 nM, and 1 μM) were added to cells. After 2 hours of exposure to Compound 1 or DMSO, $VEGF_{165}$ (R&D Systems, Minneapolis, MN; catalog# 293VE050) was added to a final concentration of 100 ng/ml; no VEGF was added to samples that are subsequently referred to as the "baseline" samples. After a 10-min, 8 hr, 24 hr and 48h VEGF stimulation the conditioned medium was filtered through 0.45 μM syringe filter from Pall Gelman Laboratory (Ann Arbor, MI catalog# 4560) and immediately frozen on dry ice. Conditioned media was stored at –70°C until subsequent analysis.

Analysis of Conditioned Media by 2D gel electrophoresis

[0282] Thawed conditioned media samples were precipitated with three volumes of acetone for 2 hours at -20°C, then centrifuged at 13000 RPM for 15 minutes. Pellets were washed with the 2D Clean-Up Kit (Amersham, Cat. # 80-6484-51) as per protocol, air dried for three minutes, then resuspended in 8M urea (Amersham), 100 mM dithiothreitol (Fisher), 4% CHAPS (3[(cholamidopropyl)dimethylammonio]propanesulfonate from Calbiochem), and placed in a thermomixer (Eppindorf) at 600 RPM and 25°C for 2 hours. Protein was quantitated with Bio-Rad Protein Assay (cat# 500-0006) using the microassay for cuvettes protocol.

[0283] Samples were diluted to 0.3 μg/μl with IEF Buffer containing 1% IPG Buffer pH 3-10 (Amersham). Eighteen centimeter IPG strips pH 3-10 (Amersham) were rehydrated with 120 μg sample (400 μL) under Drystrip Cover Fluid (Amersham) on the IPGphor (Amersham) at 20°C for 18 hours. Strips were focused with the following program:

200 volts for 1 hour, ramped from 200 volts to 1000 volts over two hours, held at 1000 volts for 1 hour, ramped from 1000 volts to 8000 volts over 6 hours, then held at 8000 volts for 10 hours. Polyacrylamide gels were hand cast in the Hoeffer DALT multi-gel casting chamber (Amersham) at 10% Acrylamide (Bio-Rad 40% Acrylamide Solution), 2.67% piperazine diacrylamide (Bio-Rad), 0.375 M tris, pH 8.8 (Bio-Rad), 0.075% ammonium persulfate (Bio-Rad), and 0.075% TEMED (N, N, N', N'-tetramethylethylenediamine). Gels were over-layed with water-saturated butanol (Fisher), and left to polymerize at room temperature overnight.

[0284] Focused strips were equilibrated for ten minutes with gentle shaking in 10 milliliters Equilibration Buffer: 6 M Urea (Fisher), 50 mM tris-HCl pH 8.8 (Fisher), 30% glycerol (Fisher), 2% SDS (Fisher) with 1% dithiothreitol followed by ten minutes in Equilibration Buffer with 4% iodoacetamide.

[0285] The equilibrated strips were loaded onto the gel surfaces and sealed with hot agarose overlay solution containing 0.5% agarose in 50 mM tris-HCl pH 6.8, 2% SDS.

[0286] Gels were run in the Hoeffer DALT tank (Amersham) in 25 mM tris (Fisher), 192 mM glycine (Fisher), and 0.1% SDS overnight at 100 volts and 8°C.

[0287] The gels were washed three times in 500 mL Fixative (10% methanol and 7% glacial acetic acid) for one hour each with gentle agitiation. The gels were then stained overnight in 500 mL Sypro Ruby Protein Gel Stain (Molecular Probes). Gels were again washed three times in 500 mL fixative for an hour each with gentle agitiation. Images were obtained on the Fluor S MultiImager (Bio-Rad) using transilluminated ultraviolet light for 45 seconds with the 520LP emission filter. Image analysis was done using PDQuest version 7.0.1 (Bio-Rad).

2D Gel Spot Cutting

[0288] The automated gel cutting was performed using the ProteomeWorks Spot Cutter (BioRad, Hercules, CA) and PDQUEST (v.7.0.1) software. Three sets of 2D gels were cut (Table 14). Based on the gel imaging analysis, the same spots of all three gels were combined in the same well of a 96-well plate.

Protein In-gel Digestion

[0289] The automated digestion was performed using Investigator ProGest Digestion Station (Genomic Solutions). The sample plate (96-well pink plate) was placed onto the reaction block. A white sample collection plate was placed onto the collection block. The method used, Ruby48proGestv1, was based on the software ProGest Method Editor (v.1.1.0.29). Then the samples were digested automatically with trypsin (0.19 μg/well) at 37 °C for overnight.

MALDI-TOF-MS Analysis

[0290] After in-gel digestion, the digest was concentrated and desalted by using C18 reversed phase Ziptip (Millipore, Bedford, MA). Bound peptides were eluted with 4 μL matrix solution (a-cyano-4-hydroxycinnamic acid in acetonitrile/0.1%TFA 1:1 v/v).

[0291] 1 μL eluted solution was spotted onto the MALDI target. Peptide mass mapping was performed on an ABI Voyager STR matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometer (Applied Biosystems, Framingham, MA). The acceleration voltage was 20 kv, the grid voltage was 14kv, the extraction delay time was 300nsecexternal calibration during mass spectrometry data acquisition was used. The acquired peptide mass mapping spectra was processed and analyzed by Data Explorer software (Version 4.0.0.0.). The internal calibration was performed by using trypsin autolysis peptide mass 842.5099 and 2211.1046.

MALDI-MS/MS Analysis

[0292] The MALDI-MS/MS analysis was performed using API Qstar Pulsar equipped with oMALDI Source (PE Sciex). The curtain gas was 25, the declustering potential was 45, the focusing potential was set from range 220 to 250 V various by samples. CAD gas was 7 and collision energy was at 35 to 100 depending on samples. The ion energy was set at 1 kV. Data acquisition and processing was done using Analyst QS and oMALDI Server (v. 2.2) softwares. The biomaker identification was obtained with MASCOT database search using MS/MS spectra. The publically accessible link to the "MASCOT" tool for protein identification using peptide data is:
<www.matrixscience.com/cgi/index.pl?page=/search_form_select.html>.

ELISA Analysis

[0293] Reagents for human pro-Matrix Metalloproteinase 1 (pro-MMP-1) ELISA kits were obtained from R& D Systems, Inc. (Minneapolis, MN; catalog # DMP100). ELISAs were performed on conditioned media samples according to the manufacturers' instructions. The optical density of each well was determined using a universal microplate spectrophotometer (μQuant) from Bio-Tek Instruments, Inc. (Winooski, VT). KC-4 software from Bio-Tek Instruments, Inc. was used to extrapolate cytokine concentrations from the standard curves.

2. Additional studies using Compound 1 – Results

2D Gel Analysis of Conditioned Media from VEGF +/- Compound 1 Treated HUVECs.

[0294] Conditioned media isolated from HUVECs pre-treated with vehicle (DMSO) or Compound 1 (1uM) and subsequently stimulated with VEGF for 24 and 48 hours or baseline, untreated samples were analyzed by 2D gel analysis (see Materials and Methods). This analysis identified 1 spot (#1202) whose abundance consistently increased with addition of VEGF in two separate gel runs and appeared to decreased with Compound 1 pre-treatment, although not consistently using this technology (Table 15). These spots were excised and underwent MALDI and MALDI-MS/MS analysis for subsequent protein identification.

Identification of Interstitial Collagenase Precursor/pro-MMP1 By Database Search Based On Peptide Mass Fingerprint Spectra.

[0295] Peptide mass fingerprint data sets were analyzed by searching SwissProt protein database with ProteinProspector MS-Fit (Version 3.2.1). The searches were set with the following parameters, Human Mouse (Species), 1-66 kDa (molecular weight range), trpysin used for digest, maximum one missed cleavage, mass tolerance 50 ppm. Methionine was set as modified by oxidation and cysteine was set as modified by carbamidomethylation. Peptides were considered with hydrogen at N terminus and free acid at C terminus. The peptide masses were monoisotopic. The database search result was significant if the protein was ranked as the first hit and the sequence coverage was more than 30%, in addition a MOWSE score higher than 1e+003 (MS-Fit) was required. As summarized in Table 16 and

Table 17, Spot 1202 was definitively identified as interstitial collagenase precusor (pro-MMP1).

ELISA Analysis of pro-MMP1 Levels in HUVEC Conditioned Media

[0296] Because the quantitation of pro-MMP1 levels in 2D gels is only semi-quantitative (and therefore less consistent), the levels of pro-MMP-1 in HUVEC conditioned media were also assayed using a quantitative ELISA assay. The ELISA analysis indicated that levels of pro-MMP1 increase quantitatively when HUVEC cells are treated with VEGF and are decreased with pre-incubation of Compound 1 at 10nM, 100nM or 1uM concentrations (Table 18).

Pro-MMP1 Levels in Plasma from Compound 1 Treated Patients in Study B

[0297] Pro-MMP1 levels in the plasma of Study B patients after treatment with Compound 1 (day 1 pre-treatment, day 1 24 hr post-treatment, day 13 pre-treatment, day 13 12 hr post-treatment, and day 13 24 hr post-treatment) was analyzed. The results (see Table 19) demonstrate that pro-MMP1 levels increased in the plasma of patients after they received Compound 1.

J. EXAMPLES – MORE STUDIES USING COMPOUND 1

1. More studies using Compound 1 – Materials and Methods

Plasma Samples

[0298] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site.

[0299] Plasma samples were then thawed and centrifuged to remove particulate matter (10 min @ 5000 x g). The resulting supernatants were collected and split into aliquots and were re-frozen at –80 °C. Prior to assay, samples were thawed, Immunoglobulin Inhibiting Reagent (IIR, Bioreclamation Inc) was added to a final concentration 0.25 mg/mL, and Tween 20 was added to final concentration of 0.1%.

Antibody chip microarray manufacture

[0300] Glass slides were cleaned and derivatized with 3-cyanopropyltriethoxysilane. The slides were equipped with a Teflon mask, which divided the slide into sixteen 0.65 cm diameter wells or circular analysis sites called subarrays. Printing was accomplished with a Perkin-Elmer Spotarray Enterprise non-contact arrayer equipped with piezoelectric tips, which dispense a droplet (~350 pL) for each microarray spot. Antibodies were applied at a concentration of 0.5 mg/mL at defined positions. Each chip was printed with sixteen copies of one type of array, either Array 1.1 or Array 2.1 (see below). Both arrays consist of capture antibodies against different analytes and are defined by the antibody set contained. Analytes measured using both arrays are listed in Table 20.

Array 1.1 detector set.

Analyte	Name
ANG	Angiogenin
BLC (BCA-1)	B-lymphocyte chemoattractant
EGF	Epidermal growth factor
ENA-78	Epithelial cell-derived neutrophil-activating peptide
Eot	Eotaxin
Eot-2	Eotaxin-2
Fas	Fas (CD95)
FGF-7	Fibroblast growth factor-7
FGF-9	Fibroblast growth factor-9
GDNF	Glial cell line derived neurotrophic factor
GM-CSF	Granulocyte macrophage colony stimulating factor
IL-1ra	Interleukin 1 receptor antagonist
IL-2 sRα	Interleukin 2 soluble receptor alpha
IL-3	Interleukin 3
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IL-13	Interleukin 13
IL-15	Interleukin 15
MCP-2	Monocyte chemotactic protein 2
MCP-3	Monocyte chemotactic protein 3
MIP-1α	Macrophage inflammatory protein 1 alpha
MPIF	Myeloid progenitor inhibitory factor 1
OSM	Oncostatin M
PlGF	Placental growth factor

Array 2.1 detector set.

Analyte	Name

AR	Amphiregulin
BDNF	Brain-derived neurotrophic factor
FLT-3 Lig	fms-like tyrosine kinase-3 ligand
GCP-2	Granulocyte chemotactic protein 2
HCC4 (NCC4)	Hemofiltrate CC chemokine 4
I-309	I-309
IL-1α	Interleukin 1 alpha
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-17	Interleukin 17
MCP-1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony stimulating factor
MIG	Monokine induced by interferon gamma
MIP-1β	Macrophage inflammatory protein 1 beta
MIP-1γ	Macrophage inflammatory protein 1 delta
NT-3	Neurotrophin 3
NT-4	Neurotrophin 4
PARC	Pulmonary and activation-regulated chemokine
RANTES	Regulated upon activation, normal T expressed and presumably secreted
SCF	Stem cell factor
sgp130	Soluble glycoprotein 130
TARC	Thymus and activation regulated chemokine
TNF-RI	Tumor necrosis factor receptor I
TNF-α	Tumor necrosis factor alpha
TNF-β	Tumor necrosis factor beta
VEGF	Vascular endothelial growth factor

Microarray Chip Physical Quality Measures

[0301] Each print run of microarray chips was assigned a unique Production Sheet Number, and the RCAT immunoassay run for this print run was documented. For each print run, printed slides were subjected to the following control measures: (1) two slides, one from the start and one from the end of the run, were inspected

using light microscopy. If the percentage of missing spots observed was greater than 5%, then the batch failed and the slides were discarded immediately. For all print runs described herein, 100% of the printed spots were present on slides selected for this examination; and (2) for each print run, two of the printed slides were examined by a Cy5-labeled goat-anti-mouse antibody (GAM-Cy5). Since the majority of capture antibodies in these arrays were of mouse origin, this procedure examined total antibody attachment and provided a rapid measure of surface and binding uniformity. To account for differences in binding efficiency for different capture antibodies, the intensities of all spots for each individual capture antibody were measured across the chip (4 spots/subarray, 64 spots/chip) and a %CV was calculated for that feature. The average of these %CVs for all quantified capture antibodies must be below 20% for the print batch to pass. Chips treated with GAM-Cy5 were also checked for missing spots after the assay and if the percentage of missing spots was greater than 5%, then the batch failed (for these studies 100% of the printed spots were still present after this assay). Following these QC measures, qualified slides were stored at 4°C until used.

Reagent Quality Control Measures

[0302] The assay suite was considered as consisting of the microarray chips, detector antibodies and the reagents required for the RCAT portion of the assay. There were validation procedures for these reagents individually as well as a functional validation of the entire set. Reagents used in the RCA portion of the assay were from reserved vendor lots where possible. Materials produced in-house were subjected to QC procedures and qualified on microarray chips before release. If lot numbers changed for a particular reagent that is supplied by an outside vendor, the new lots were qualified by comparison with existing qualified stocks.

[0303] For each array type, a concentrated batch of detectors was prepared which consisted of a mixture of biotinylated antibodies directed against all analytes represented by an array. A functional QC was then performed for each detector antibody batch by carrying out the standard RCAT assay on a specially prepared sample set. Mixtures of 2-3 different cytokines were prepared so as to provide a high intensity signal and applied to 14 wells of a chip (with each well being treated with a different mixture up to the total complement of detector antibodies) and two arrays

were used as blank controls. The chips were developed and scanned and the resulting signals were compared to the positional map of the particular array. This examination demonstrated that the stock detector mixture was complete and the features were active. Once a detector batch had passed this QC, it was distributed into smaller volumes and released for use in the assay.

Positional and Functional Quality Measures

[0304] Following printing, a set of microarray chips was validated in concert with the qualified reagents discussed above. This was a two-part quality control measure. The first portion was identical to the detector antibody qualification procedure just described. In this case, the high intensity signals were compared to the array map and the proper positioning of capture antibody replicates was verified. The second test was a functional QC for all analytes of a specified array using known sample matrices. Normal human serum (Jackson ImmunoResearch Laboratories, Code#009-000-121) and heparinized plasma were assayed neat or spiked with purified recombinant cytokines representing all analytes in the array. Spiked mixtures were then titrated down the subarrays of a slide from 5,000 pg/ml to 20 pg/mL of spiked cytokine concentrations along with three subarrays for each un-spiked control sample. The data was quantified and for every analyte in the array a titration curve was generated to show that the feature intensity was above background and exhibiting increasing intensity with increasing analyte concentrations.

RCA Immunoassay

[0305] Prior to assay, the slides were removed from storage at room temperature in sealed containers and opened in a humidity controlled chamber (35-40%). Blocking was done by submerging the slides in a Coplin jar filled with blocking buffer (Seablock, Pierce Chemical Co., 1:1 dilution with 1X PBS) pre-chilled to 4°C, and placing the Coplin jar in a 37°C incubator for 1 hour. The slides were then washed twice (2 min per wash) in 60 mL of 1x PBS/0.5% Brj-35 washing buffer. On each slide, control serum (Jackson ImmunoResearch Laboratories) was applied to one subarray, plasma control applied to two subarrays, and a negative control with PBS buffer applied to two subarrays. The test samples were assayed on the remaining 11 subarrays. Twenty microliters of the treated sample were then

applied to each subarray. The basics of performing immunoassays with RCA signal amplification has been described (*Nat. Biotechol.* (2002) 20:359-65) and we are using SOPs derived from the protocols used in that study. Slides were scanned (GenePix 4000B, Axon Instruments Inc.) at 10 μm resolution with a laser setting of 100% and a PMT setting of 550 V. Mean pixel fluorescence values were quantified using the fixed circle method in GenePix Pro 4.0 (Axon Instruments). Using proprietary software, the fluorescence intensity of microarray spots was analyzed for each feature and sample, and the resulting mean intensity values were determined. Dose-response curves for selected cytokines were examined, ensuring that feature intensity is above background and exhibiting increasing intensity with increasing analyte concentration.

ELISA Analysis

[0306] Reagents for FLT3 ligand (FL) and IL-6 ELISA kits were obtained from R& D Systems, Inc. (Minneapolis, MN; catalog #s DFK00, Q6000). C-reactive protein (CRP) (accession ID AAA 52075) ELISA kits were obtained from KMI Diagnostics (Minneapolis, MN; catalog #EU59131). ELISAs were performed on patient plasma according to the manufacturers' instructions. The FL and CRP kits relied on a colorimetric readout; the optical density of each well was determined using a microplate spectrophotometer and data was analyzed using KC-4 software from Bio-Tek Instruments, Inc. The IL-6 kit was a chemiluminescent sandwich ELISA; luminescence values were determined on a microplate luminometer. SOFTmaxPRO software was used to extrapolate cytokine concentrations from the standard curves.

2. More studies using Compound 1 – Results

Plasma markers identified using Antibody chip technology

[0307] A multiplex antibody chip based approach (MSI, Molecular Staging Inc.) was used to identify plasma biomarkers of compound 1. Plasma samples harvested from 3 advanced malignancy patients pre and post Compound 1 treatment (Phase I trial A) were used for this analysis. Twenty three of 108 markers tested, showed changes following Compound 1 treatment (day 28). These are listed in Table 21. Controls included normal donor plasma which did not show significant changes

in these markers. Each of these is a potential biomarker of Compound 1, and may reflect drug exposure, biological activity or efficacy.

[0308] A number of markers showing the most dramatic changes and/or of known biological significance were further investigated (specifically VEGF, PLGF, IL-6, IL-8 and MCP-1). The relative changes were validated by ELISA on the same patient samples assessed in the antibody chip screen, and both methods showed good concordance (Table 22). Several of these markers had previously been identified by ELISA analysis on compound 1 treated samples, (PLGF, VEGF, IL-6), and several were novel (FLT3 ligand and MCP-1). Additional data on FLT3 ligand levels tested in an expanded set of patients is provided in Figure 25. Dramatic induction was observed following Compound 1 treatment in all cases.

Plasma ELISA Studies

[0309] In an effort to identify novel biomarkers of exposure to Compound 1, plasma samples were analyzed from 18 patients enrolled in Trial B. Plasma was taken both before study (D1 PRE) as well as at the end of the first cycle of treatment (Day 28 POST). Each time point was measured in triplicate and the standard deviation from the mean was calculated. Both the mean value and standard deviation for each patient at each time point is shown graphically in Figure 25. It was found that 100% of the patients exhibited an increase in FLT3 ligand (FL) concentration from day 1 to day 28. In 14 out of 18 patients, the increase was more than four-fold. The increase in FLT3 ligand concentration is attributed to treatment with Compound 1.

Plasma ELISA Studies – Fatigue Corrolation

[0310] To find biomarkers that correlated with fatigue, plasma samples were analyzed from 62 patients enrolled in trials for Compound 1. Samples were taken before study (D1) and either two or four weeks after the start of cycle 1 dosing (Day 13 for trials B, C and D and Day 28 for A and E). The patients are grouped according to their highest recorded fatigue grade (0-4 scale from the NCI Common Toxicity Criteria). As seen in Figure 26, there is a statistically significant difference between the increases in IL-6 seen in patients with low fatigue (Grade 1 or 0) and those with

moderate to high fatigue (Grade 3 or 4), p=0.001. Thus, a patient who exhibits a large change in IL-6 plasma concentration (greater than two-fold) after treatment with Compound 1 has a much higher chance of experiencing a high degree of fatigue (Grade 3 or 4) than a patient whose IL-6 level remains more stable.

[0311] Plasma samples were further analyzed from 18 patients enrolled in Trial B for Compound 1. Samples were taken before study (D1) and two weeks after the start of cycle 1 dosing (D13). As shown with IL-6 levels, the patients are grouped according to their highest recorded fatigue grade (0-4). See Figure 27. It was determined there is a statistically significant difference in C-reactive protein (CRP) (accession ID AAA 52075) induction between patients with little fatigue (Grade 0, 1, or 2) and those with moderate to severe fatigue (Grade 3 or 4), p = 0.0088. Therefore, patients with a greater than two-fold increase in C-reactive protein after treatment with Compound 1 are more prone to experiencing high fatigue than those who have smaller fold changes in CRP.

Plasma ELISA Studies –Corrolation to biological response and/or clinical efficacy

[0312] Levels of C-reactive protein were measured as described above for the experiments involving CRP and fatigue. ELISAs were performed on plasma samples from patients before treatment (i.e., baseline values). The patients' samples and results were divided into two groups based upon observed clinical outcome. Patients with stable disease (SD pts) were defined as patients on study for over 6 months. Patients with progressive disease (PD pts) were defined as patients who had come off study due to disease progression or lack of efficacy in fewer than 6 months. This separation of patients demonstrated that patients with progressive disease had much higher baseline levels of CRP than those patients who were stable (median values of 63.8 μg/mL vs. 6.5 μg/mL, respectively) (Figure 28). If a patient were to have a baseline level of CRP of above 20 μg/mL before treatment, that patient has a greater chance of rapidly progressing than if the level of CRP were below 20 μg/mL. Thus, CRP is a baseline marker of biological response and/or clinical efficacy.

K. EXAMPLES – COMPOUND 1 STUDIES OF OB-CADHERIN 1 PROTEIN

1. Compound 1 studies of OB–cadherin 1 protein – Materials and Methods

Tumor samples

[0313] Colo205 human colon xenograft tumors were isolated and fixed in Streck Tissue Fixative (Streck Laboratories, Inc., La Vista, NE). Samples used in immunohistochemistry were sent out to BioPathology Sciences Medical Corporation (South San Francisco, CA) for paraffin embedding and sectioning.

Antibodies

[0314] A rabbit polyclonal antibody recognizing the cytoplasmic tail region of OB-cadherin 1 (cadherin 11) was purchased from Zymed Laboratories, Inc. (Zymed reagent #71-7600; South San Francisco, CA).

Immunohistochemistry

[0315] Sections (4-5 μm) stained using an automated immunohistochemistry system (Benchmark System, Ventana Medical Systems, Inc., Tucson, Arizona). In brief, slides were deparaffinized using heat at 75°C and Ventana's EZ Prep product (Ventana reagent #950-102). Antigen retrieval was performed by incubating the slides for 30 min with Ventana's CC2 product (Ventana reagent #950-123), a citrate-based solution with pH 6.0. Primary antibody (5 μg/ml) was incubated for 24 min at room temperature, followed by a secondary detection system, using biotinylated secondary antibody (Vector anti-rabbit secondary, BA-1000, at 2.5 μg/ml; Vector Laboratories, Burlingame, CA) with incubation time of 8 min. Streptavadin-horseradish peroxidase with 3, 3′ diaminobenzidine as a substrate were used in conjunction with the secondary detection system. All samples analyzed for OB-cadherin 1 expression were also stained with the omission of primary antibody as a negative control.

2. Compound 1 studies of OB–cadherin 1 protein – Data Summary

[0316] As expression of OB-cadherin 1 (cadherin 11) RNA was found to be up-regulated at 24 hour post-Compound 1 treatment (see Table 12), effects on OB-cadherin 1 expression at the protein level was also examined. Colo205 xenograft tumors were isolated from Compound 1-treated mice at 24 and 48 hours post treatment. Tumors were fixed in formalin and sections were isolated and processed for immunohistochemistry (IHC).

[0317] Tissue sections were stained with an antibody that recognizes OB-cadherin 1. As a negative control, adjacent sections were processed similarly but with the omission of a primary antibody. This analysis identified up-regulation of OB-cadherin 1 protein in Colo205 tumors treated with Compound 1 for 24 and 48 hours as compared to vehicle treated samples (Figure 29).

TABLES

Table 1.

	Number of samples from which RNA was processed	Number with RNA yield >1ug, at both d1 and d56	Number hybridized to U95A chips	Number for which data passed Quality Control inspection for further analysis
SU5416				
CR	0	0	0	0
PR	13	8	6	6*
MR	6	3	2	1
SD	6	5	1	1
PD	10	7	6	5*
Control				
CR	1	1	1	1*
PR	9	5	5	5*
MR	4	1	1	0
SD	3	2	2	2
PD	11	9	7	6*
Total:	63	41	31	27

*** These samples were included in the dataset used in detailed analysis**

Table 2.

Affymetrix number	Gene name/ Symbol	Putative function(s)	Increased in SU5416 arm	Increased in Control arm
34546_at	Defensin α 4	Corticostatic, Ca channel regulator	10 of 11	6 of 12
33530_at	CEA CAM 8	Tumor antigen, integral membrane protein.	9 of 11	4 of 12
37054_at	BPI	Anti-pathogen response	9 of 11	4 of 12
31859_at	MMP-9	Protease; ECM maintainence	8 of 11	2 of 12
32821_at	Lipocalin 2	Anti-pathogen response; apoptosis	10 of 11	5 of 12
34319_at	S100 P	Ca-binding protein	9 of 11	3 of 12
41249_at	Hypothetic. Protein FLJ13052	unknown	7 of 11	1 of 12
1962_at	Liver arginase	Amino acid metabolism	9 of 11	3 of 12
266_s_at	CD24 antigen	Anti-pathogen response; differentiation of B cells	9 of 11	0 of 12
31506_s_at	Defensin α 3	Chemotaxis; anti-microbial response	10 of 11	4 of 12
32275_at	Antileuko-protease	Secreted inhibitor of serine proteases	9 of 11	4 of 12
115_at	Thromobospondin 1	Blood clotting; angiogenesis	9 of 11	3 of 12
37149_s_at	Lactoferrin	Iron transport; putative protease	11 of 11	5 of 12

Table 3.

Gene	Forward Primer	Reverse Primer
Thrombospondin 1	TTGGCTACCAGTCCAGCAGC (SEQ ID NO: 1)	GGGTTGGTGTCCCAGTAGGA (SEQ ID NO: 2)
MMP-9	CCCGGAGTGAGTTGAACCA (SEQ ID NO: 3)	CCTAGTCCTCAGGGCACTGC (SEQ ID NO: 4)
Defensin α 3	CCCAGAAGTGGTTGTTTCCCT (SEQ ID NO: 5)	GTCCATGTTTTTCCTTGAGCCT (SEQ ID NO: 6)
Lactoferrin	CTGGAAGCCTGTGAATTCC (SEQ ID NO: 7)	GAATGGCTGAGGCTTTCTTGG (SEQ ID NO: 8)
Lipocalin-2	GCTGACTTCGGAACTAAAGGAGAA (SEQ ID NO: 9)	TGGGACAGGGAAGACGATGT (SEQ ID NO: 10)
CD24	CTGCCTCGACACACATAAACCTT (SEQ ID NO: 11)	CATCTAAGCATCAGTGTGTGACC A (SEQ ID NO: 12)

Table 4.

	P-value of Mann-Whitney U Test	
Gene	Affymetrix (n = 23)	SYBR Green RT-PCR (n = 31)
MMP-9	0.0025	0.0748
Thrombospondin 1	0.0267	0.7186
CD24	0.0006	0.0057
Defensin α 3	0.0002	0.2196
Lactoferrin	0.0002	0.0065
Lipocalin-2 (LCN2)	0.0005	0.0057

Table 5.

Gene	n	Rank Sum (Treatment)	Rank Sum (Control)	Mann-Whitney U	p-value
MMP-9	36	415	251	0.0095	
CD24	36	443	223	0.0005	
Lactoferrin	36	460	206	0.0001	
LCN2	36	419	247	0.0065	

Table 6.

Predictor Gene Set for discriminating between the control and Compound B arms: LCN2, CD24, Lactoferrin

1. All cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	6	30	83
Total	32	35	84

2. Jackknifed classification matrix for all cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	8	28	78
Total	34	33	81

3. Prediction subset (randomly selected 34 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	13	1	93
Treatment	4	16	80
Total	17	17	85

4. Validation subset (randomly selected 33 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	11	6	65
Treatment	5	11	69
Total	16	17	67

Table 7.

Trial C patients 1-23 PLGF plasma level ratios

Patient #	d1 (6 hr):d1 (0 hr)	d29:d1	d42:d1	
1	0.695512	1.871238	0.398897	
2	2.050289	11.96579	1.040025	
3	1.965517	3.586207	1.206897	
4	1.985061	24.72922	1.985061	
5	1.09557	11.3316	1.09557	
6	1.800672	11.02117	1.365586	
8	1.16493	12.38985	1.157115	
10	1.622462	>10	2.652309	
11	1.250022	7.511615	1.386382	
13	1.038442	1.817441	NA	***Note: d15:D1 ratio is 6.4 for pt. 13
15	0.896403	6.651554	1.189041	
17	0.907692	19.21308	1.134385	
18	1.007357	12.30822	1.105295	
20	1.2261	11.29078	1.598445	
21	1.518564	14.84205	0.955559	
22	1	2.423462	0.815385	
Average	**1.326537**	**10.19689**	**1.272397**	

Table 8.

	MIG				IP-10		
Patient	day 1	day 15	end C1 dosing	Ratio	day1	end C1 dosing	Ratio
11 (B)	41.927		739.71	17.64281	55.617	>500	>9
1	48.375		1066.2	22.04031	64.847	>500	>7.7
11	34.432		344.93	10.01772	65.32	384.06	5.879669
17	166.8		907.09	5.438189	72.29	>500	>6.9
24	80.751		314.2	3.890973			
26	80.751		995.47	12.32765	64.296	>500	>7.7
27	80.826		81.439	1.007584			
7	106.04		145.64	1.373444	139.2	240.31	1.726365
20	161.91		698.23	4.312458	73.67	>500	>6.9
22	37.685	339.16		8.999867			
9 (A)	60.393		138.56	2.294306			

	I-TAC			
Patient	day 1	day 15	end C1 dosing	Ratio
11 (B)	428.83		>4000.0	>9
1				
11				
17				
24	259.38		771.04	2.972627
26	97.917		701.46	7.163822
27	139.94		315.69	2.255895
7				
20				
22	190.76	2020.2		10.59027
9 (A)	59.975		212.26	3.539141

Table 9.

Patient #	PLGF Ratio (end dosing:d1)	VEGFR2 ratio (end dosing:d1)	Primary Diagnosis
Trial C			
1	1.871237941	*0.265856292*	Synovial Sarcoma
2	*11.96579454*	*0.25171334*	Rectal
3	*3.586206897*	*0.5673112*	Gall-bladder
4	*24.72921991*	*0.34236691*	Hepatocellular
5	*11.33159926*	*0.406890612*	Melanoma
6	*11.02116835*	*0.572980623*	Breast
7	*23.86685363*	*0.404286499*	Ovary
8	*12.38984817*	*0.318366334*	Small Cell Lung
10	*10*	*0.45614753*	Melanoma
11	*7.511615487*	*0.323681006*	Met. Colon
13	1.817440506	*0.460416464*	Renal Cell Carcinoma
14	*3.080408542*	*0.575703582*	Met. Melanoma
15	*6.651553529*	*0.506347193*	Renal Cell Carcinoma
17	*19.21307692*	*0.177452364*	NSCLC
18	*12.30822285*	*0.271285002*	NSCLC
20	*11.29078149*	*0.385479698*	Colon
21	*14.84205128*	*0.369637606*	Breast
22	2.423461538	*0.479139734*	Sarcoma
23	1	*0.504789782*	Sarcoma
24	0.99016936	*0.457140878*	met. Rectal carcinoma
25	*12.03862173*	*0.250133543*	Retropero Sarcoma
26	*13.29469461*	*0.493391074*	Met Pelvis Sarcoma
29	*5.237072177*	*0.59927457*	SCCR R) Parotid
30		*0.519969363*	Colon AdenoCA
31		*0.330647033*	Lung AdenoCA
Trial A			
1		*0.565173104*	Renal Cell Carcinoma
3		*0.597994214*	Bronchial adeno.
4		*0.685465839*	breast carcinoma
5	*12.97391648*	*0.182557005*	uterine
6	*25.082632*	*0.458079657*	pelvic angiosarcoma
7		*0.648790016*	pleural mesothelioma
8		*0.64392508*	uterine
9		*0.38520981*	Bronchial adeno.
10	*5.301660143*	*0.44915001*	colorectal
13		*0.297438475*	neuroendocrine

Table 9. cont.

Patient #	PLGF Ratio (end dosing:d1)	VEGFR2 ratio (end dosing:d1)	Primary Diagnosis
Trial D			
1		***0.502083475***	GIST
3	2.98130415	***0.670742516***	GIST
4	***5.228142589***	0.972905837	GIST
5	1.351061278	***0.616277438***	GIST
6	***7.055260831***	***0.684932856***	GIST
13	***4.095209935***	***0.600072917***	GIST
14	***4.786806356***	***0.685754939***	GIST
15	***22.29951691***	0.767346939	GIST
16	***3.034877351***	0.727153597	GIST
18	***16.89889246***	***0.471077781***	GIST
19	2.782095462	***0.542935245***	GIST
20	***12.47129736***	***0.598602839***	GIST
21	***11.56450225***	***0.351218422***	GIST
22	2.996492067	***0.644054653***	GIST
Trial B			
4		***0.67109839***	Head & Neck
5		***0.678411145***	CRC
6		***0.4130696***	thymic
7		***0.301532905***	CRC
8		***0.456886687***	thyroid
9		***0.597322954***	thyroid

Table 10.

MIG

Patient #	day 1	day 15	end C1 dosing	Ratio	Cancer Type
11 (B)	41.927		739.71	17.64281	Pancreatic
1	48.375		1066.2	22.04031	Synovial Sarcoma
11	34.432		344.93	10.01772	Met. Colon
17	166.8		907.09	5.438189	NSCLC
24	80.751		314.2	3.890973	Met. Rectal
26	80.751		995.47	12.32765	Pelvis Sarcoma
20	161.91		698.23	4.312458	Colon
22	37.685	339.16		8.999867	Sarcoma
9 (A)	60.393		138.56	2.294306	Bronchial Adeno.

Table 11A.

Transcript Name	**Putative Role**	**Accession No.**	**Time Point (hrs)**	**Fold Change *Increase***
Basic transcription factor 3 homologue	Transcription factor	M90354	6	2.1
c-jun proto oncogene	Transcription factor	J04111	6	2.5
c-fos cellular oncogene	Transcription factor	K00650	6	4.2
Tyrosine phosphatase non-receptor type 2	Protein phosphatase	NM_080422	6	2.2
cdc2-related protein kinase	Cell cycle regulation	M68520	6	19
Cyclin C	Cell cycle regulation	M74091	6	2.5
DNA polymerase gamma	DNA polymerase	U60325	6	7.3
Basic transcription factor 3 homologue	Transcription factor	M90354	24	2.2
Protein kinase C alpha	Protein kinase	X52479	24	3.0
Lipocortin II/annexin A2	Ca^{++} -regulated membrane binding protein	D00017	24	2.3
Histone H2B, member R	Transcriptional regulation	AF531293	24	3.0
Amphiregulin	Growth factor	NM_001657	24	6.1

Table 11A cont.

Transcript Name	**Putative Role**	**Accession No.**	**Time Point (hrs)**	**Fold Change *Decrease***
Ephrin receptor EphB4	Tyrosine kinase receptor	NM_004444	6	2.5
Hanukah factor/Granzyme A	Serine protease	M18737	24	2.3
von Hippel-Lindau (VHL) tumor suppressor	Tumor suppressor	NM_000551	24	3.7
OB-cadherin 1	Ca^{++}-dependent cell adhesion protein	D21254	24	2.2
OB-cadherin 2	Ca^{++}-dependent cell adhesion protein	D21255	24	2.0
Phosphoinositol 3-phosphate-binding protein-3 (PEPP3)	Phosphoinositide-binding protein	NM_014935	24	2.1
Phosphoinositol 3-kinase, p85 subunit	Proliferation	M61906	24	2.2
Mucin 1	Adhesion, cell-cell interaction	J05582	24	2.5
Hepatitis C-associated microtubular aggregate p44	Interferon-induced protein	Exon 1-9 D28908, D28909, D28910, D28911, D28912, D28913, D28914, D28915	24	2.0
ErbB3/HER3 receptor tyrosine kinase	Growth factor receptor	M29366	24	2.1

Table 11B.

Transcript Name	**Putative Role**	**Accession No.**	**Time Point (hrs)**	**Fold Change *Increase***
Vinculin	Cell adhesion	M33308	4	2.5
Basic transcription factor 3	Transcription factor	M90357	24	2.2
Phosphoinositol 3-kinase, p110 subunit	Proliferation	NM_006219	24	4.5
Transcript Name	**Putative Role**	**Accession No.**	**Time Point (hrs)**	**Fold Change *Decrease***
Gelsolin	Actin binding protein	X04412	4	2.1
Cyclin D2	Transcription	NM_001759	4	2.2

Table 12.

Transcript Name	Accession No.	Relative Expression Level (6 hr)	Relative Expression Level (24 hr)
Amphiregulin	NM_001657	1.9	2.5
Cdc2-related protein kinase	M68520	0.43	0.55
Phosphoinositol 3-kinase, p110 subunit	NM_006219	0.59	1.6
Cyclin C	M74091	842	22.3
OB-cadherin 1	D21254	0.35	23.8
OB-cadherin 2	D21255	0.40	0.51
Phosphoinositol 3-kinase, p85 subunit	M61906	1.0	2.30
Mucin 1	J05582	0.32	1.13
von Hippel-Lindau tumor suppressor	NM_000551	0.9	0.55
Ephrin receptor, EphB4	NM_004444	3.5	3.1
Gelsolin	X04412	4.0	0.04

Table 13.

Transcripts	GenBank Accession No.	Forward Primer (5′ - 3′)	Reverse Primer (5′ - 3′)	Taqman Probe (5′ - 3′)
Amphiregulin	NM_001657	ATGATGAGTCGGTCCTCT TTCC (SEQ ID NO: 13)	TGACAATTGAAAGTTTAA AACCATCATA (SEQ ID NO: 14)	TCCATTGTCTTATGA TCCAC (SEQ ID NO: 15)
CDK-2 related protein	M68520	AGTTAGAAGTTAGGGTTT AGGCATCATT (SEQ ID NO: 16)	TACCCATGCCCTCACTCA ATC (SEQ ID NO: 17)	AAGTGTCAGCATTCT CAA (SEQ ID NO: 18)
PI3-kinase, p110	NM_006219	CCAGTGTTGTGAGGATGC ATATC (SEQ ID NO: 19)	CAGTCAACATCAGCGCAA AGA (SEQ ID NO: 20)	ATTCCCATGCCGTCG TA (SEQ ID NO: 21)
PI3-kinase, p85	M61906	CAAACCTACTGTATCTCT AATACAGTGTGACT (SEQ ID NO: 22)	GACAGAGATGATTATCCC TTTAAACCA (SEQ ID NO: 23)	AGCGCTCACCTTTG (SEQ ID NO: 24)
Cyclin C	M74091	CCTACAGACAGACATACA TAGACATTTCAA (SEQ ID NO: 25)	ATTATGCTTCATGTTTCCT GGCTTA (SEQ ID NO: 26)	CCAAATTAAGAAAT ATTATACTAATCA (SEQ ID NO: 27)
OB-cadherin 1	D21254	GACAACAGTTCTGAGCTG TAATTTCG (SEQ ID NO: 28)	TGGGTTTAAGCTGGCTGA ATATTAT (SEQ ID NO: 29)	ACTCTGGACACTCTA TATGT (SEQ ID NO: 30)
OB-cadherin 2	D21255	TCAGCCAGCTTAAACCCA TACAA (SEQ ID NO: 31)	TGGCACGTATTAGTTTAA GATGAAAGTAG (SEQ ID NO: 32)	CTTGTTACTGCTGAT TCT (SEQ ID NO: 33)
Mucin 1	J05582	TTCAGAGGCCCCACCAAT T (SEQ ID NO: 34)	CCCACATGAGCTTCCACA CA (SEQ ID NO: 35)	TCTCGGACACTTCTC (SEQ ID NO: 36)

Table 13 cont.

Transcripts	GenBank Accession No.	Forward Primer (5′ - 3′)	Reverse Primer (5′ - 3′)	Taqman Probe (5′ - 3′)
VHL tumor suppressor	NM_000551	TGAGGCAGGGACAAGTCTTTCT (SEQ ID NO: 37)	ACCCTGACTGAAGGCTCATGA (SEQ ID NO: 38)	CTCTTTGAGACCCCAGTGC (SEQ ID NO: 39)
EphB4	NM_004444	TCTACCGTCCTTGTCATAACTTTGTG (SEQ ID NO: 40)	ATGATGATGGGCCCCTGTT (SEQ ID NO: 41)	CCTTTGCCCAAGTTG (SEQ ID NO: 42)
Gelsolin	X04412	TGGACGTTTTGTGATCGAAGAG (SEQ ID NO: 43)	AAGTCAAGGCTTCTGTCTTTTCTTCT (SEQ ID NO: 44)	CTTGAGAATCCTTTCCAACC (SEQ ID NO: 45)

Table 14.

Gel No. 1	VEGF + DMSO - 48hr
Gel No. 2	Compound 1 + VEGF + DMSO - 48hr
Gel No. 3	VEGF + DMSO - 48hr

Table 15.

Spot #1202	**Run #1**	**Run #2**
Sample		
baseline	126	22.5
VEGF at 24h	437	192.4
VEGF at 48h	812	540
VEGF and compound 1 (1uM) at 24h	270	484.7
VEGF and compound 1 (1uM) at 48h	869	158

Table 16.

SSP	Well	MALDI Mass Mapping result	MS-Fit MOWSE Score	Sequence Coverage
1202	A6	Interstitial Collagenase Precursor	3.64E+07	31%

Table 17.

SSP	Well	Confirmed Peptide	File Name	MS/MS result	MASCOT Score
1202	A6	DIYSSFGFPR (SEQ ID NO: 46)	spotA6-1188.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	34
1202	A6	DGFFYFFHGTR (SEQ ID NO: 47)	spotA6prod1393-2.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	22

Table 18.

HUVEC SAMPLE[1]	Average pro-MMP1 (ng/ml)	Standard Deviation
VEGF 10 min	4.66	0.3079
DMSO 10 min	4.64	0.1003
compound 1@ 10 nM 10 min	5.41	0.1224
Compound 1 @ 100 nM 10 min	5.78	0.3158
Compound 1 @ 1 uM 10 min	5.04	0.331
VEGF 8 hr	16.47	1.0048
DMSO 8 hr	17.63	1.2563
Compound 1 @ 10 nM 8 hr	14.93	1.1245
Compound 1 @ 100 nM 8 hr	12.75	0.6686
Compound 1 @ 1 uM 8 hr	14.48	1.0551
VEGF 24 hr	45.71	3.06
DMSO 24 hr	79.94	4.50
Compound 1 @ 10 nM 24 hr	70.21	4.82
Compound 1 @ 100 nM 24 hr	50.26	1.24
Compound 1 @ 1 uM 24 hr	50.42	2.42
VEGF 48 hr	244.74	3.91
DMSO 48 hr	234.72	10.85
Compound 1 @ 10 nM 48 hr	135.35	1.04
Compound 1 @ 100 nM 48 hr	128.75	11.05
Compound 1 @ 1 uM 48 hr	103.09	3.60

[1]Time points indicated (10 min, 8h, 24h, 48h) refer to the period of time post-VEGF treatment after which samples were isolated.

Table 19.

	Pro-MMP1 (ng/ml)	FC vs d1 Pre[1]	% Change vs d1 Pre
Pt 3 d1 Pre[2]	0.3115		
d1 24 hr	0.2837	-1.097990835	-8.924558587
d13 Pre	0.6756	2.168860353	116.8860353
d13 12 hr	0.6235	2.001605136	100.1605136
d13 24 hr	0.4035	1.295345104	29.53451043
Pt 4 d1 Pre	0.5214		
d1 24 hr	0.8938	2.869341894	71.42309168
d13 Pre	0.6246	2.005136437	19.79286536
d13 12 hr	0.4579	1.469983949	-12.17874952
d13 24 hr	0.4514	1.449117175	-13.42539317
Pt 5 d1 Pre	0.5739		
d1 24 hr	0.323	1.036918138	-43.71841784
d13 Pre	0.7269	2.333547352	26.65969681
d13 12 hr	0.6874	2.206741573	19.77696463
d13 24 hr	0.4171	1.339004815	-27.32183307
Pt 6 d1 Pre	0.2969		
d1 24 hr	0.6818	2.188764045	129.6396093
d13 Pre	0.7597	2.438844302	155.8773998
d13 12 hr	0.7992	2.56565008	169.1815426
d13 24 hr	1.066	3.422150883	259.043449
Pt 7 d1 Pre	0.5743		
d1 24 hr	0.7334	2.354414125	27.70329096
d13 Pre	0.7374	2.367255217	28.39979105
d13 12 hr	0.5154	1.654574639	-10.25596378
d13 24 hr	0.7203	2.312359551	25.42225318
Pt 8 d1 Pre	0.2879		
d1 24 hr	0.3664	1.176243981	27.26641195
d13 Pre	1.7166	5.510754414	496.2486975
d13 12 hr	1.1071	3.554093098	284.5432442
d13 24 hr	0.8494	2.726805778	195.0329976
Pt 9 d1 Pre	0.7786		
d1 24 hr	0.4816	1.546067416	-38.14538916
d13 Pre	0.4931	1.582985554	-36.66837914
d13 12 hr	1.047	3.361155698	34.47212946
d13 24 hr	2.6022	8.353772071	234.2152582
Pt 10 d1 Pre	0.3613		
d1 24 hr	0.2396	-1.300083472	-33.68391918
d13 Pre	1.2937	4.153130016	258.0680875
d13 12 hr	1.4224	4.566292135	293.6894547
d13 24 hr	1.0684	3.429855538	195.7099363

Table 19 cont.

Pt 11 d1 Pre	0.299		
d1 24 hr	0.2866	-1.08688067	-4.147157191
d13 Pre	0.6931	2.225040128	131.8060201
d13 12 hr	0.4496	1.443338684	50.36789298
d13 24 hr	1.1685	3.751203852	290.8026756
Pt 12 d1 Pre	0.8587		
d1 24 hr	0.5418	1.739325843	-36.90462327
d13 Pre	2.1689	6.962760835	152.5794806
d13 12 hr	2.1494	6.900160514	150.308606
d13 24 hr	5.9226	19.01316212	589.7170141

[1] Fold change of pro-MMP1 levels are indicated by "FC vs d1 pre". These levels were calculated by dividing the levels of pro-MMP1 after drug treatment by the MMP1 levels present before drug treatment (d1 pre).

[2] Patient number is indicated (Pt), time point of sampling is indicated pre-treatment (d1 pre), 24 hours post first treatment (d1 24h), after 13 days of treatment (d13 pre), after 13 days and 12 hours post-treatment (d13 12h), and 13 days and 24hours of treatment (d13 24h).

Table 20.

5000 ng/mL Bio-mIgG	4000 ng/mL Bio-mIgG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mIgG	3000 ng/mL Bio-mIgG	2000 ng/mL Bio-mIgG
5000 ng/mL Bio-mIgG	4000 ng/mL Bio-mIgG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mIgG	3000 ng/mL Bio-mIgG	2000 ng/mL Bio-mIgG
5000 ng/mL Bio-mIgG	4000 ng/mL Bio-mIgG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mIgG	3000 ng/mL Bio-mIgG	2000 ng/mL Bio-mIgG
5000 ng/mL Bio-mIgG	4000 ng/mL Bio-mIgG	BLANK	AR	BDNF	FGF-6	Flt3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mIgG	3000 ng/mL Bio-mIgG	2000 ng/mL Bio-mIgG
1000 ng/mL Bio-mIgG	800 ng/mL Bio-mIgG	600 ng/mL Bio-mIgG	400 ng/mL Bio-mIgG	300 ng/mL Bio-mIgG	200 ng/mL Bio-mIgG	100 ng/mL Bio-mIgG	80 ng/mL Bio-mIgG	60 ng/mL Bio-mIgG	50 ng/mL Bio-mIgG	40 ng/mL Bio-mIgG	30 ng/mL Bio-mIgG	20 ng/mL Bio-mIgG	10 ng/mL Bio-mIgG	5 ng/mL Bio-mIgG	Blank
1000 ng/mL Bio-mIgG	800 ng/mL Bio-mIgG	600 ng/mL Bio-mIgG	400 ng/mL Bio-mIgG	300 ng/mL Bio-mIgG	200 ng/mL Bio-mIgG	100 ng/mL Bio-mIgG	80 ng/mL Bio-mIgG	60 ng/mL Bio-mIgG	50 ng/mL Bio-mIgG	40 ng/mL Bio-mIgG	30 ng/mL Bio-mIgG	20 ng/mL Bio-mIgG	10 ng/mL Bio-mIgG	5 ng/mL Bio-mIgG	Blank
1000 ng/mL Bio-mIgG	800 ng/mL Bio-mIgG	600 ng/mL Bio-mIgG	400 ng/mL Bio-mIgG	300 ng/mL Bio-mIgG	200 ng/mL Bio-mIgG	100 ng/mL Bio-mIgG	80 ng/mL Bio-mIgG	60 ng/mL Bio-mIgG	50 ng/mL Bio-mIgG	40 ng/mL Bio-mIgG	30 ng/mL Bio-mIgG	20 ng/mL Bio-mIgG	10 ng/mL Bio-mIgG	5 ng/mL Bio-mIgG	Blank
1000 ng/mL Bio-mIgG	800 ng/mL Bio-mIgG	600 ng/mL Bio-mIgG	400 ng/mL Bio-mIgG	300 ng/mL Bio-mIgG	200 ng/mL Bio-mIgG	100 ng/mL Bio-mIgG	80 ng/mL Bio-mIgG	60 ng/mL Bio-mIgG	50 ng/mL Bio-mIgG	40 ng/mL Bio-mIgG	30 ng/mL Bio-mIgG	20 ng/mL Bio-mIgG	10 ng/mL Bio-mIgG	5 ng/mL Bio-mIgG	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-1δ	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-1δ	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-1δ	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-1δ	NAP-2

Table 21.

Patient	1, 2, 3	Patient	1, 2, 3
• ENA-78	(-) ↓ ↓	TNFR1	↑ ↑ (-)
• MPIF-1	(-) (-) ↓	VEGF	↑ ↑ (-)
• GCP-2	↑ (-) (-)	Flt3L	↑ ↑ ↑
• Amphireg	↑ (-) (-)	PLGF	↑ ↑ (-)
• IL-1α	↑ ↑ (-)	IL6	↑ ↑ (-)
• IL-1β	↑ ↑ (-)	MCP-1	↑ ↑ (-)
• IL-2	↑ ↑ (-)	TNFα	↑ ↑ (-)
• MIG	(-) ↓ (-)	TARC	↑ (-) (-)
• NT4	↑ (-) ↑	MMP7	↑ ↑ ↓
• GCP-2	↑ ↑ (-)	MMP9	(-) (-) ↑
• IGFBP-1	↑ ↑ ↑	leptin	(-) ↑ (-)
• GRO-β	↑ (-) ↑		

Table 22.

	Patient 1		Patient 2		Patient 3	
	ELISA	**Ab Chip**	**ELISA**	**Ab Chip**	**ELISA**	**Ab Chip**
VEGF	32	2.7	72	4.3	3	1.8
PLGF	13	4.6	25.1	21.7	5.3	1.6
IL-6	29	2.9	11.6	3.7	0.9	0.99
IL-8	2	1.5	2.7	1.8	0.77	1.7
FLT3 L	10.3	13.9	6.7	7.7	2.6	6.2
MCP-1	2.2	2.5	1.93	2	1.0	1.4

We claim:

1. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

2. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

3. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

4. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-

cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

5. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-

binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal is responding to the compound that inhibits tyrosine kinase activity.

6. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo

sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

7. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb

gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

8. A method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic

transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in the same type of mammal without cancer, the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

9. The method of any one of claims 1-8, wherein the mammal is a human, rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate or monkey.

10. The method of any one of claims 1-8, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one mammalian biological tissue from the mammal.

11. The method of claim 10, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

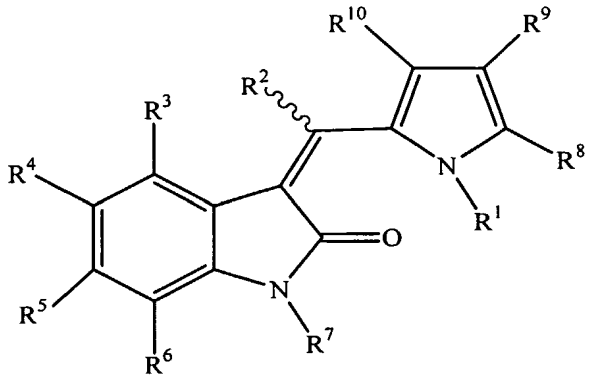
12. The method of claim 10, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

13. The method of any one of claims 1-8, wherein the mammal has cancer.

14. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is an indolinone compound.

15. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is:

a pyrrole substituted 2-indolinone having the formula:



wherein:

R^1, R^2 and R^7 are hydrogen;

R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

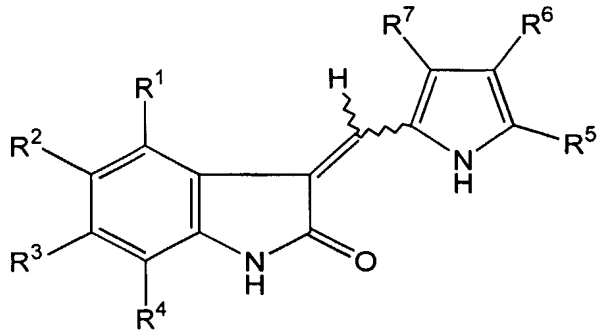
R^8 is unsubstituted lower alkyl;

R^9 is $-(CH_2)(CH_2)C(=O)OH$; and

R^{10} is unsubstituted lower alkyl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cyclkoalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_rR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14,}$ $-S(O)_2NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$,
$-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5, R^6 or R^7 must be $-C(O)R^{10}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl and aryl;

R^{10} is selected from the group consisting of hydroxy, alkoxy, aryloxy, $-N(R^{11})(CH_2)_nR^{12}$, and $-NR^{13}R^{14}$;

R^{11} is selected from the group consisting of hydrogen and alkyl;

R^{12} is selected from the group consisting of $-NR^{13}R^{14}$, hydroxy, $-C(O)R^{15}$, aryl, heteroaryl, $-N^{+}(O^{-})R^{13}R^{14}$, $-N(OH)R^{13}$, and $-NHC(O)R^{a}$ (wherein R^{a} is unsubstituted alkyl, haloalkyl, or aralkyl);

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^{13} and R^{14} may combine to form a heterocyclo group;

R^{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R^{16} is selected from the group consisting of hydroxy, $-C(O)R^{15}$, $-NR^{13}R^{14}$ and $-C(O)NR^{13}R^{14}$;

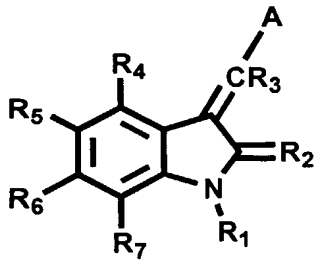
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R^{20} is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R_1 is H;

R_2 is O or S;

R_3 is hydrogen;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, and CONRR';

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-

oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$ or CONRR';

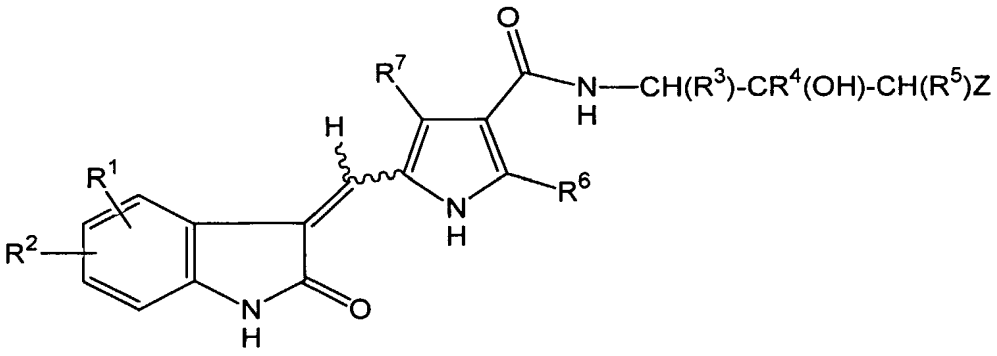
n is 0-3;

R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, $-C(O)R^8$, $-NR^9R^{10}$ and $-C(O)NR^{12}R^{13}$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)R^8$, $-S(O)_2NR^9R^{10}$ and $-SO_2R^{14}$ (wherein R^{14} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^3, R^4 and R^5 are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently hydrogen or alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are attached from a heterocycloamino group;

R^6 is selected from the group consisting of hydrogen or alkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and $-C(O)R^{17}$ as defined below;

R^8 is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

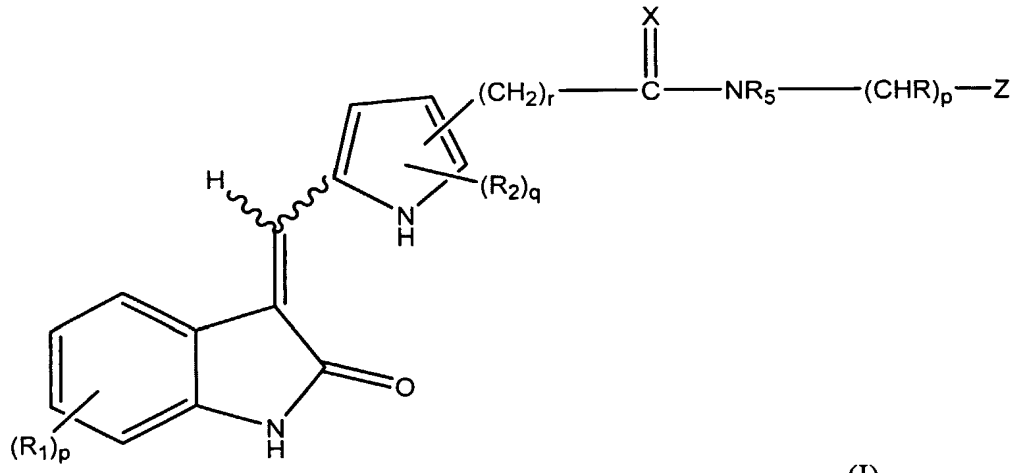
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound A) or a pharmaceutically acceptable salt thereof.

17. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one (Compound B) or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula I:



(I),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8, -NR_9R_{10}, -$NR_9C(O)$-R_{12} and –$C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, –C(O)-R_8, and SO_2R'', where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8 and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

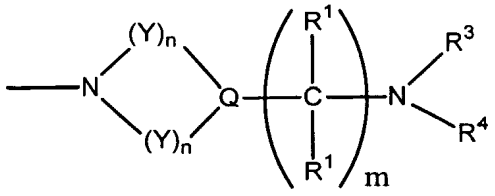
R_8 is selected from the group consisting of –OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of –OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or –NR_3R_4, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2, N, O and S or



wherein Y is independently CH_2, O, N or S,

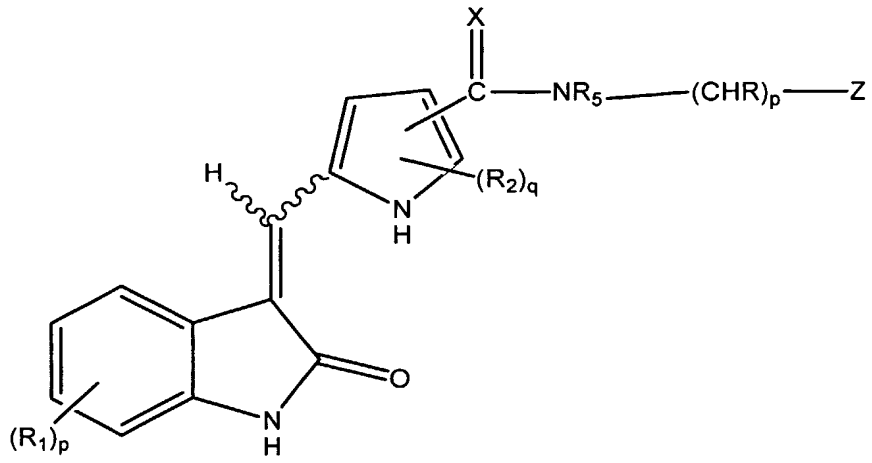
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

19. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula II:



(II),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R_1 is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8, -NR_9R_{10}, -$NR_9C(O)$-R_{12} and –$C(O)NR_9R_{10}$;

each R_2 is independently selected from the group consisting of alkyl, aryl, heteroaryl, –C(O)-R_8, and SO_2R'', where R'' is alkyl, aryl, heteroaryl, NR_9N_{10} or alkoxy;

each R_5 is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R_8 and $(CHR)_rR_{11}$;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

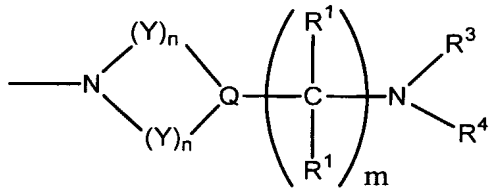
R_8 is selected from the group consisting of –OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of –OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2, N, O and S or



wherein Y is independently CH_2, O, N or S,

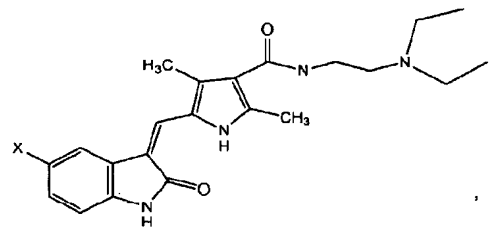
Q is C or N;

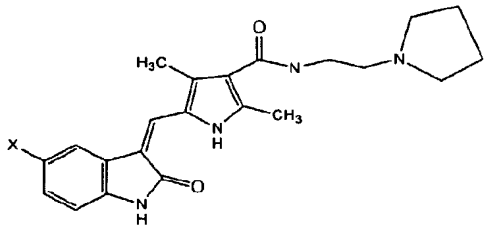
n is independently 0-4; and

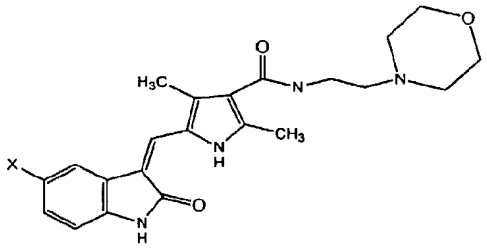
m is 0-3;

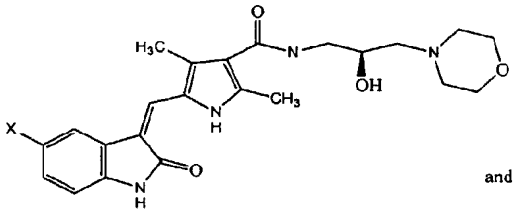
or a pharmaceutically acceptable salt thereof.

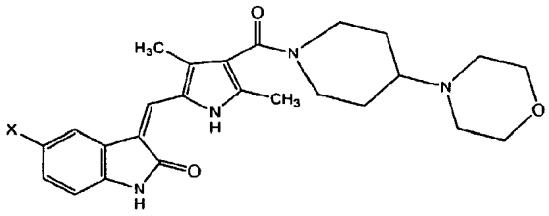
20. The method of claim 18, wherein the compound that inhibits tyrosine kinase activity is selected from the group consisting of:


,


,


,


and



wherein X is F, Cl, I or Br;

or a pharmaceutically acceptable salt thereof.

21. The method of claim 18, wherein the compound of Formula I is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1).

22. A kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein

A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

23. A kit of claim 22, wherein said instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor elF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal

phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1α, IL-1β, IL-2, NT4, GCP-2, IGFBP-1, GRO-β, TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFα, TARC, MMP7, leptin, pro-MMP1 (interstitial collegenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

24. A method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

25. The method of claim 24, wherein the tyrosine kinase inhibitor is a compound of Formula I or salt thereof.

26. The method of claim 25, wherein the compound of Formula I or salt thereof is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1) or salt thereof.

27. A method of claim 24, wherein the adverse event is debilitating fatigue.

28. The method of claim 24, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one biological tissue from the mammal.

29. The method of claim 24, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

30. The method of claim 24, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

FIGURES

Figure 1.

Percent Change in Plasma Proteins 12 hr post 2nd dose /pre-dose												
				SU6668.004 BID (Tablets) Plasma/Pharmacokinetics for Day 1								
Pt #	SU6668 Dose (mg/m^2)	cancer type	gender	SU6668 Cmax (ug/mL)	Tmax hrs	Exposure >2.3 ug/mL (hrs)	AUC ug*hr/mL	PAI-1	VEGF	MMP-9	TIMP-1	TF
28	400	prostate	M	13.0	15.0	21.3	164.3	297		46	27	21
32	300	ovarian	F	12.9	2.0	11.8	85.7	19	94	-45	-3	19
34	300	laryngeal	M	11.6	3.5	10.7	136.4	63	-1	156	-2	-5
17	200	colon	F	11.5	2.0	11.0	66.1	221			105	24
25	300	colon	M	11.0	2.0	13.4	75.5	7	-27	184	69	22
27	400	colon	M	10.3	6.0	9.1	71.2	-40	10	-15	-5	32
19	200	leiomyosarcoma	F	9.5	4.0	12.8	80.2	104	95	36	-0.2	-12
23	300	renal	F	9.3	2.0	8.0	53.5	-69	-36	-79	9	9
16	200	thyroid	F	9.3	2.0	7.3	55.7	263		409	43	37
24	300	leiomyosarcoma	F	8.2	4.0	16.4	71.2	62	9	18	-27	39
30	300	testicular	M	7.9	1.0	2.1	32.9	52	82	-66	13	-1
33	300	testicular	M	7.5	5.0	10.4	43.2	-20	121	305	99	212
31	300	hepatocellular	F	6.9	4.0	7.3	55.8	29	100	1	0	227
20	200	prostate	M	5.9	2.5	10.9	68.5	-47	181	48	-40	38
26	300	prostate	M	5.6	2.0	8.2	57.0	2	50	38	-21	8
15	200	breast	F	5.3	2.0	4.8	44.0	95	11	-1	14	9
35	300	thyroid	M	4.3	1.5	16.1	97.5	-65	24	-19	64	65
22	300	colon	M	2.5	4.0	0.5	20.8	-14	23	29	-3	5
	>500%											
	29 to 500 %											
	-66 to 28%											

Figure 2.

DIFFERENCE VALUES (percent change)

				pt 1 pre v 4 hr post d.1 200 mg/m2	pt 8 pre v 4 hr post d.1 200 mg/m2	pt 9 pre v 4 hr post d.1 200 mg/m2	pt 10 pre v 4 hr post d.1 200 mg/m2	pt 12 pre v 4hr post d. 1 200 mg/m2	pt 1 d1 pre vs 4 hr post 800 vs 200 mg/m2	pt 1 pre-dose d 28vs d1 pre-dose 200 mg/m2
			Cmax (ug/ml)	16.4	2.5	7.4	15.8	15.1	27	8.9
			AUC_{0-24} (ug hr/ml)	94.7	36.2	50.2	148.4	102.4	175.3	57.2
			Exposure>2.3 ug/ml (hrs)	13.2	2.2	6.6	19.8	12.5	20.6	9.7
CLASS	spot#	pI	MW							
1	5	5.79	140776	104	12	79	16	46	204	0

Difference= (1- spot% sample X/ spot% sample ref)(-100)

Duplicate gels were run for each (pre and post) sample. Averaged values were used for the calculations.

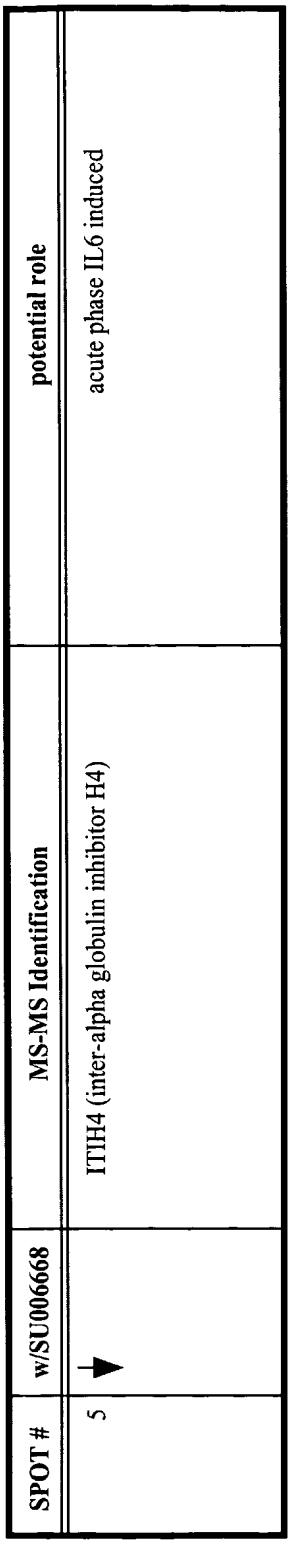
- is up in post versus pre

+ is down in post versus pre

IEF with pH 4-8 ampholines. Fifty ng of IEF standard tropomyosin added to each sample before loading.

SDS slb gels are 10%.

Figure 3.



SPOT #	w/SU006668	MS-MS Identification	potential role
5	↓	ITIH4 (inter-alpha globulin inhibitor H4)	acute phase IL6 induced

Figure 4A.

	Patient #	*017*	*019*	*022*	*027*	*028*
Gene Name	**Accession #**	**Taq/Affy F.C.**	**Taq/Affy F.C.**	**Taq/Affy F.C.**	**Taq/Affy F.C.**	**Taq/Affy F.C.**
VEGF	AF022375	3.51/ND	1.49/0.8	1.68/ND	2.91/0.5	0.27/0.198
MAPK Kinase3	L36719	1.14/0.65	0.26/2.56	0.75/0.67	0.54/1.96	0.21/0.39
PECAM	L34657	0.72/ND	0.99/0.60	1.01/ND	0.75/0.92	0.22/0.23
Hemoglobin Epsilon 1	AI349593	ND/1.53	ND/3.05	ND/ND	ND/3.06	ND/2.9
Vinculin	M33308	32.19/1.96	1.43/0.75	1.71/1.21	1.84/0.62	8.24/3.72

[1]Normalized against 18S
F.C. = Fold Change
ND = Not detected

Table 4B.

Patient #	**Taqman/Affy Fold Change**	**SU6668 Dose (mg/m2)**	**SU6668 Cmax (μg/ml)**	**SU6668 AUC (μg*hr/ml)**	**SU6668 Exposure >2.3 μg/ml (hrs)**	**Tumor Types**
17	**32.19/1.96**	200 BID	11.5	66.1	11	Colon/Rectal
27	**1.84/0.62**	400 BID	10.3	71.2	9.1	Colon/Rectal
28	**8.24/3.72**	400 BID	13	164.3	21.3	Prostate

Figure 5.

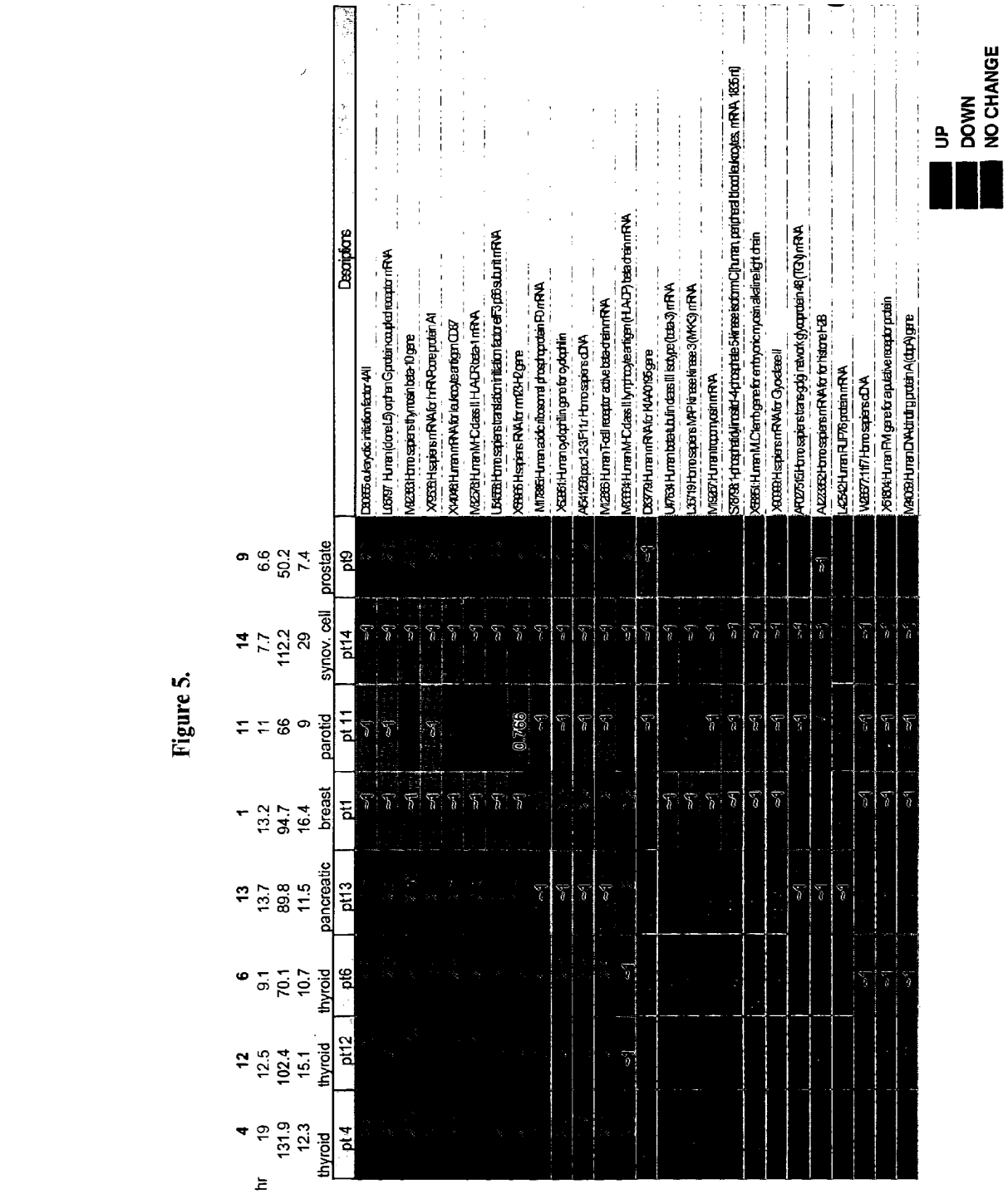

patient
exposure >2.3 ug/ml hr
AUC0-24 (ug hr/ml)
Cmax (ug/ml)
diagnosis
4
19
131.9
12.3
thyroid
12
12.5
102.4
15.1
thyroid
6
9.1
70.1
10.7
thyroid
13
13.7
89.8
11.5
pancreatic
1
13.2
94.7
16.4
breast
11
11
66
9
parotid
14
7.7
112.2
29
synov. cell
9
6.6
50.2
7.4
prostate
pt 4
pt12
pt6
pt13
pt1
pt 11
pt14
pt9
Descriptions
UP
DOWN
NO CHANGE

Figure 6.

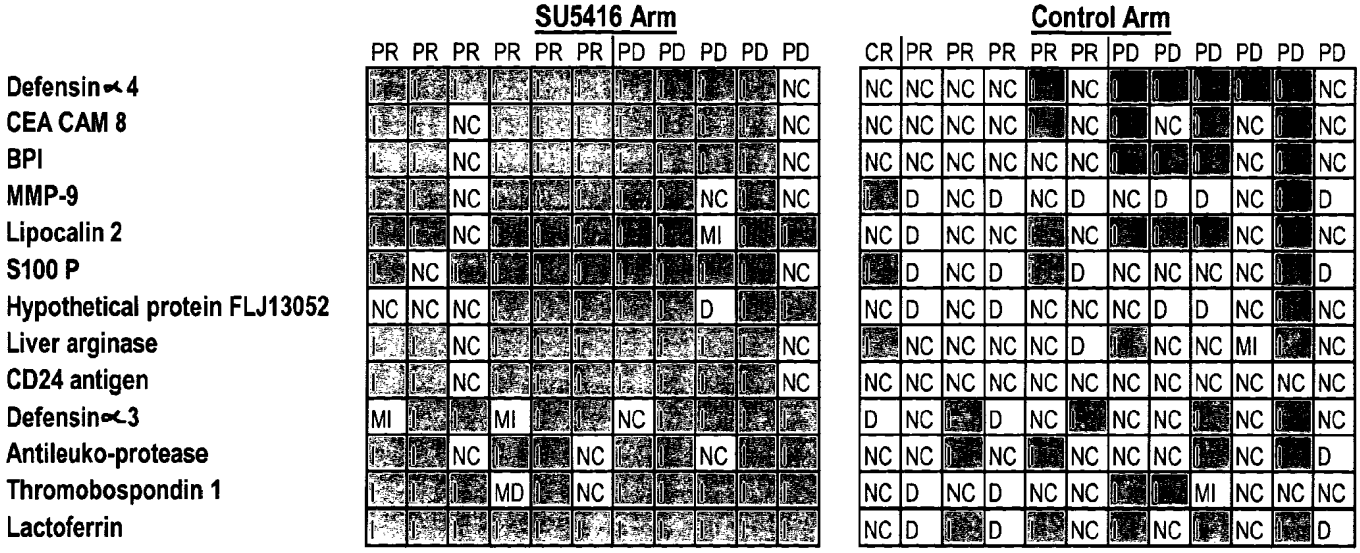
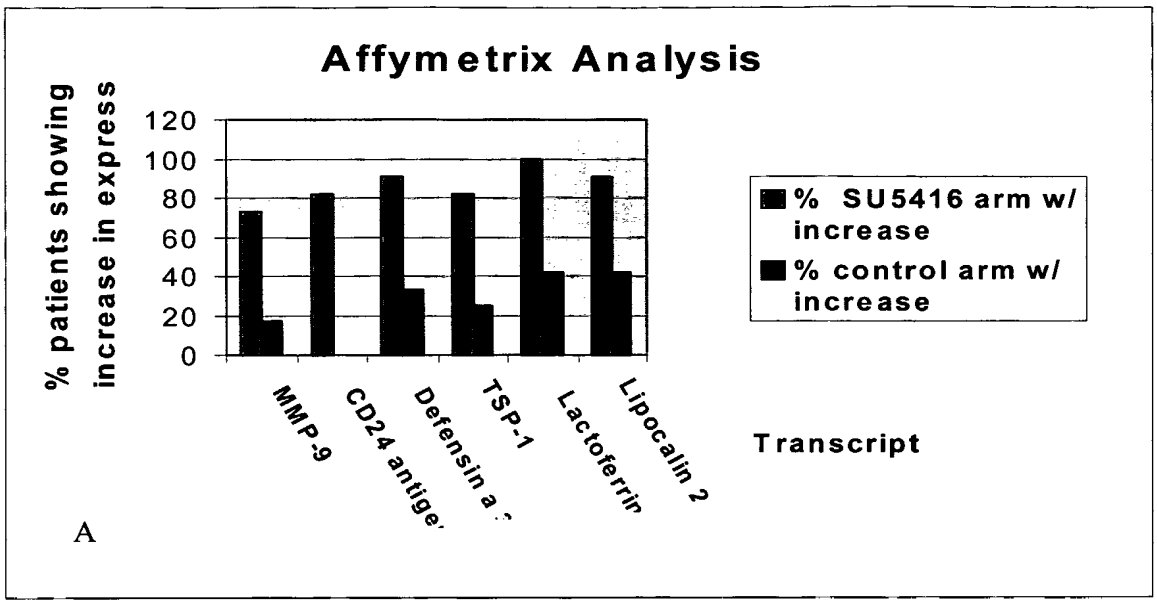

SU5416 Arm
Control Arm
PR PR PR PR PR PR PD PD PD PD PD
CR PR PR PR PR PR PD PD PD PD PD PD
Defensin∝4
CEA CAM 8
BPI
MMP-9
Lipocalin 2
S100 P
Hypothetical protein FLJ13052
Liver arginase
CD24 antigen
Defensin∝3
Antileuko-protease
Thromobospondin 1
Lactoferrin
NC
D
MI
MD

Figure 7.


Affymetrix Analysis
% patients showing increase in express
120
100
80
60
40
20
0
MMP-9
CD24 antige
Defensin a
TSP-1
Lactoferrin
Lipocalin 2
% SU5416 arm w/ increase
% control arm w/ increase
Transcript
A

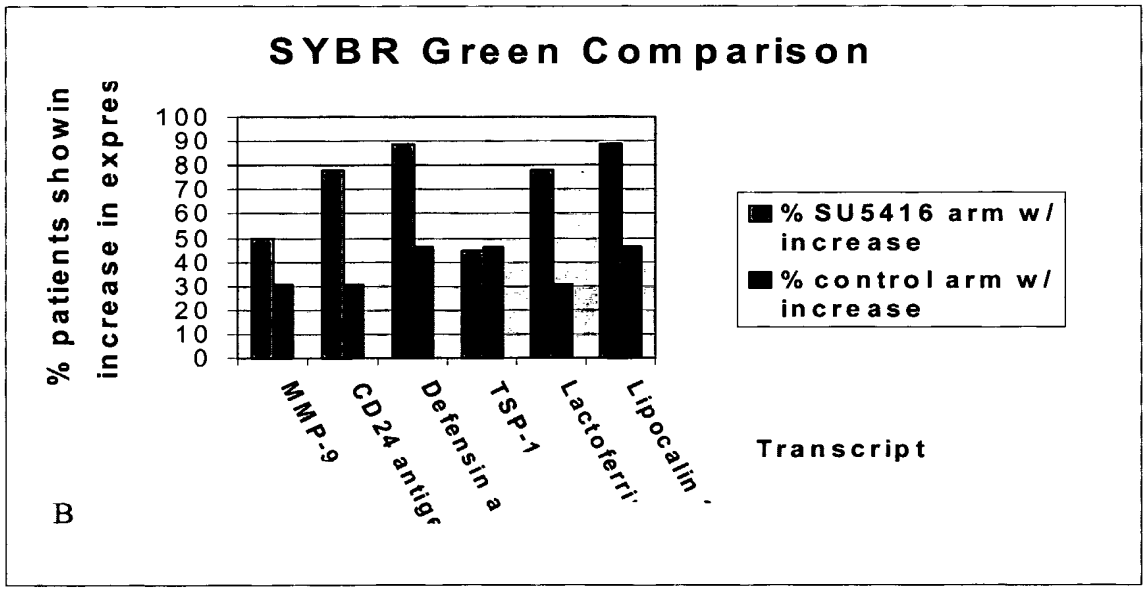

SYBR Green Comparison
% patients showin increase in expres
100
90
80
70
60
50
40
30
20
10
0
MMP-9
CD24 antige
Defensin a
TSP-1
Lactoferri
Lipocalin
% SU5416 arm w/ increase
% control arm w/ increase
Transcript
B

Figure 8.

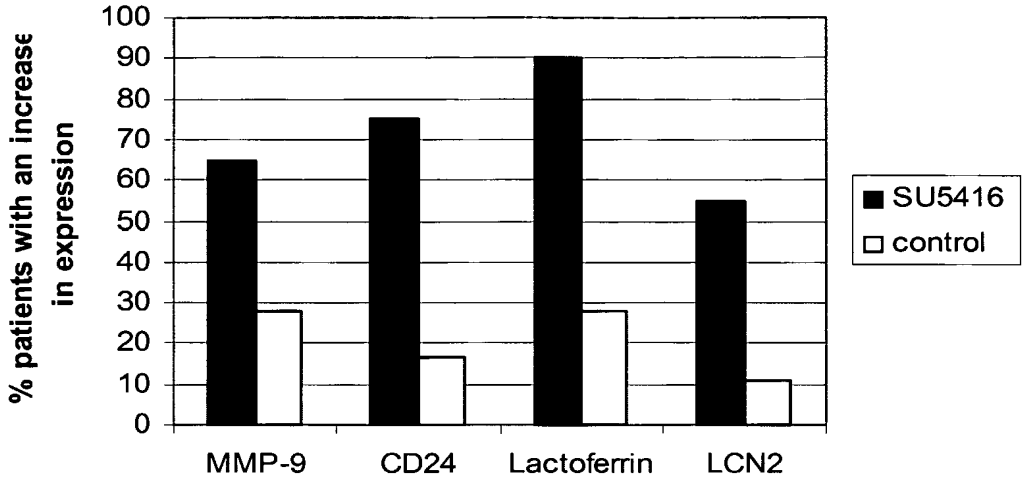

% patients with an increase in expression
100
90
80
70
60
50
40
30
20
10
0
MMP-9
CD24
Lactoferrin
LCN2
SU5416
control

Figure 9.

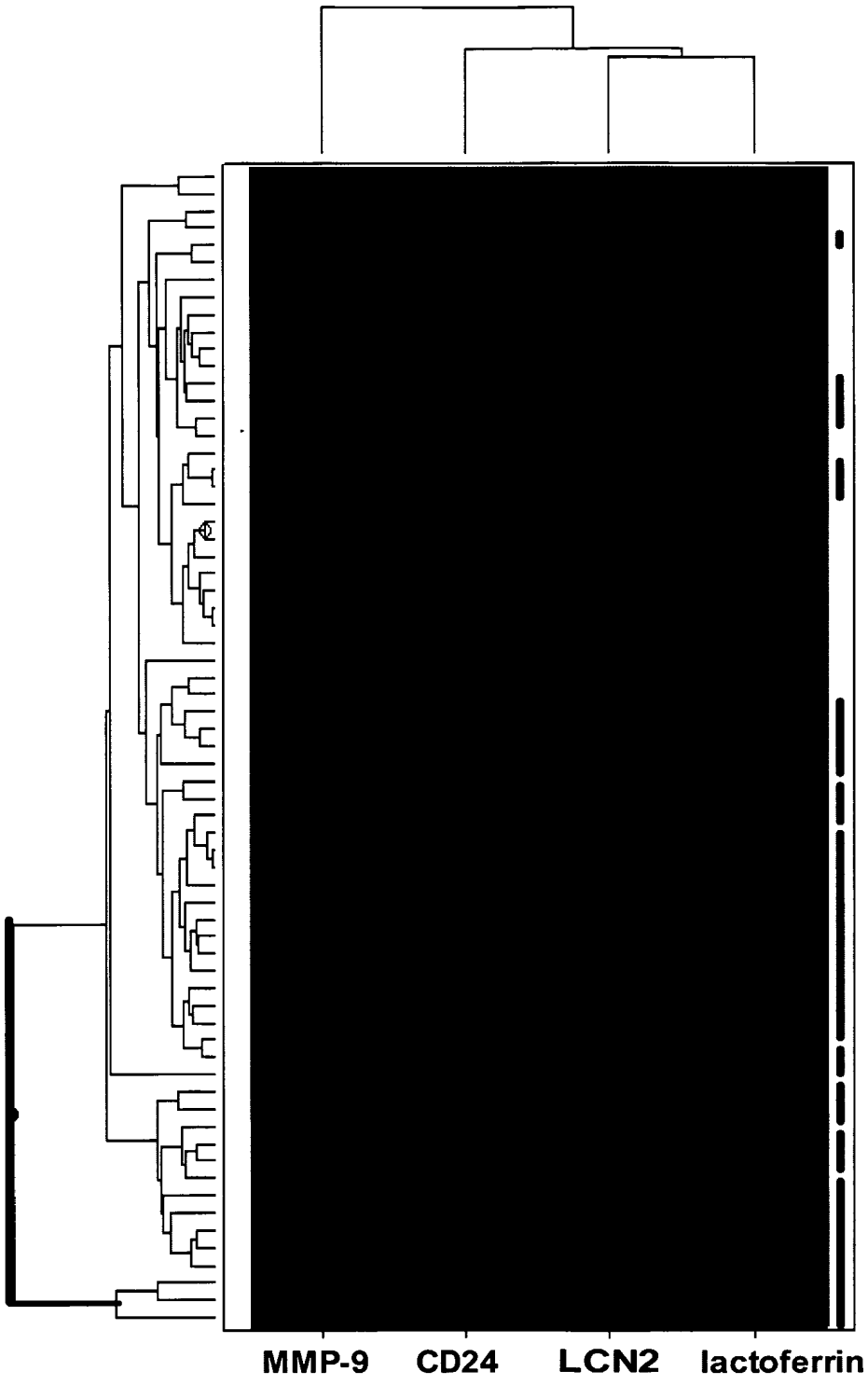
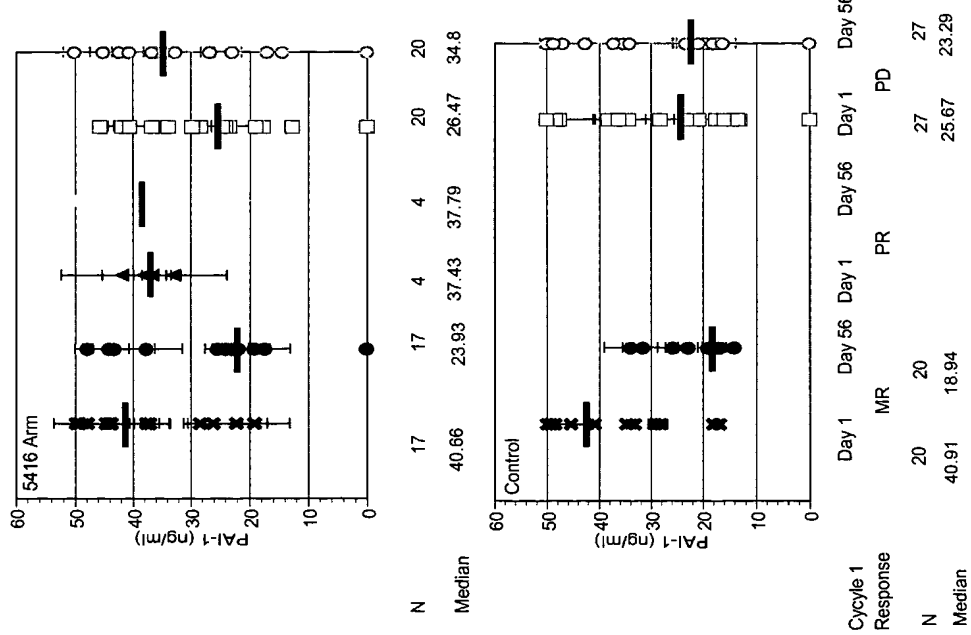


Figure 10.



Median levels of PAI-1 are indicated by a solid bar.
MR = minor response (cycle 1, PR = partial response (cycle 1), PD = progressive disease (cycle 1).

Figure 11.

mRNA and protein sequences for human lactoferrin

X53961 Human mRNA for lactoferrin [gi:34415]

1 gactcctagg ggcttgcaga cctagtggga gagaaagaac atcgcagcag ccaggcagaa
61 ccaggacagg tgaggtgcag gctggctttc ctctcgcagc gcggtgtgga gtcctgtcct
121 gcctcagggc ttttcggagc ctggatcctc aaggaacaag tagacctggc cgcggggagt
181 ggggagggaa ggggtgtcta ttgggcaaca gggcggcaaa gccctgaata aaggggcgca
241 gggcaggcgc aagtgcagag ccttcgtttg ccaagtcgcc tccagaccgc agacatgaaa
301 cttgtcttcc tcgtcctgct gttcctcggg gccctcggac tgtgtctggc tggccgtagg
361 agaaggagtg ttcagtggtg cgccgtatcc caacccgagg ccacaaaatg cttccaatgg
421 caaaggaata tgagaaaagt gcgtggccct cctgtcagct gcataaagag agactccccc
481 atccagtgta tccaggccat tgcggaaaac agggccgatg ctgtgaccct tgatggtggt
541 ttcatatacg aggcaggcct ggccccctac aaactgcgac ctgtagcggc ggaagtctac
601 gggaccgaaa gacagccacg aactcactat tatgccgtgg ctgtggtgaa gaagggcggc
661 agctttcagc tgaacgaact gcaaggtctg aagtcctgcc acacaggcct tcgcaggacc
721 gctggatgga atgtccctac agggacactt cgtccattct tgaattggac gggtccacct
781 gagcccattg aggcagctgt ggccaggttc ttctcagcca gctgtgttcc cggtgcagat
841 aaaggacagt tccccaacct gtgtcgcctg tgtgcgggga caggggaaaa caaatgtgcc
901 ttctcctccc aggaaccgta cttcagctac tctggtgcct tcaagtgtct gagagacggg
961 gctggagacg tggcttttat cagagagagc acagtgtttg aggacctgtc agacgaggct
1021 gaaagggacg agtatgagtt actctgccca gacaacactc ggaagccagt ggacaagttc
1081 aaagactgcc atctggcccg ggtcccttct catgccgttg tggcacgaag tgtgaatggc
1141 aaggaggatg ccatctggaa tcttctccgc caggcacagg aaaagtttgg aaaggacaag
1201 tcaccgaaat tccagctctt tggctccct agtgggcaga aagatctgct gttcaaggac
1261 tctgccattg ggttttcgag ggtgcccccg aggatagatt ctgggctgta ccttggctcc
1321 ggctacttca ctgccatcca gaacttgagg aaaagtgagg aggaagtggc tgcccggcgt
1381 gcgcgggtcg tgtggtgtgc ggtgggcgag caggagctgc gcaagtgtaa ccagtggagt
1441 ggcttgagcg aaggcagcgt gacctgctcc tcggcctcca ccacagagga ctgcatcgcc
1501 ctggtgctga aaggagaagc tgatgccatg agtttggatg gaggatatgt gtacactgca
1561 tgcaaatgtg gtttggtgcc tgtcctggca gagaactaca aatcccaaca aagcagtgac
1621 cctgatccta actgtgtgga tagacctgtg gaaggatatc ttgctgtggc ggtggttagg
1681 agatcagaca ctagccttac ctggaactct gtgaaaggca agaagtcctg ccacaccgcc
1741 gtggacagga ctgcaggctg gaatatcccc atgggcctgc tcttcaacca gacgggctcc
1801 tgcaaatttg atgaatattt cagtcaaagc tgtgcccctg ggtctgaccc gagatctaat
1861 ctctgtgctc tgtgtattgg cgacgagcag ggtgagaata agtgcgtgcc caacagcaac
1921 gagagatact acggctacac tggggctttc cggtgcctgg ctgagaatgc tggagacgtt
1981 gcatttgtga aagatgtcac tgtcttgcag aacactgatg gaaataacaa tgaggcatgg
2041 gctaaggatt tgaagctggc agactttgcg ctgctgtgcc tcgatggcaa acggaagcct
2101 gtgactgagg ctagaagctg ccatcttgcc atggccccga atcatgccgt ggtgtctcgg
2161 atggataagg tggaacgcct gaaacaggtg ctgctccacc aacaggctaa atttgggaga
2221 aatggatctg actgcccgga caagttttgc ttattccagt ctgaaaccaa aaaccttctg
2281 ttcaatgaca acactgagtg tctggccaga ctccatggca aaacaacata tgaaaaatat
2341 ttgggaccac agtatgtcgc aggcattact aatctgaaaa agtgctcaac ctccccccctc
2401 ctggaagcct gtgaattcct caggaagtaa aaccgaagaa gatggcccag ctccccaaga
2461 aagcctcagc cattcactgc ccccagctct tctccccagg tgtgttgggg ccttggctcc
2521 cctgctgaag gtggggattg cccatccatc tgcttacaat tccctgctgt cgtcttagca
2581 agaagtaaaa tgagaaattt tgttgatatt caaaaaaaa

Protein sequence of human lactoferrin

MKLVFLVLLFLGALGLCLAGRRRRSVQWCAVSQPEATKCFQWQR
NMRKVRGPPVSCIKRDSPIQCIQAIAENRADAVTLDGGFIYEAGLAPYKLRPVAAEVY
GTERQPRTHYYAVAVVKKGGSFQLNELQGLKSCHTGLRRTAGWNVPTGTLRPFLNWTG
PPEPIEAAVARFFSASCVPGADKGQFPNLCRLCAGTGENKCAFSSQEPYFSYSGAFKC
LRDGAGDVAFIRESTVFEDLSDEAERDEYELLCPDNTRKPVDKFKDCHLARVPSHAVV
ARSVNGKEDAIWNLLRQAQEKFGKDKSPKFQLFGSPSGQKDLLFKDSAIGFSRVPPRI
DSGLYLGSGYFTAIQNLRKSEEEVAARRARVVWCAVGEQELRKCNQWSGLSEGSVTCS
SASTTEDCIALVLKGEADAMSLDGGYVYTACKCGLVPVLAENYKSQQSSDPDPNCVDR
PVEGYLAVAVVRRSDTSLTWNSVKGKKSCHTAVDRTAGWNIPMGLLFNQTGSCKFDEY
FSQSCAPGSDPRSNLCALCIGDEQGENKCVPNSNERYYGYTGAFRCLAENAGDVAFVK
DVTVLQNTDGNNNEAWAKDLKLADFALLCLDGKRKPVTEARSCHLAMAPNHAVVSRMD
KVERLKQVLLHQQAKFGRNGSDCPDKFCLFQSETKNLLFNDNTECLARLHGKTTYEKY
LGPQYVAGITNLKKCSTSPLLEACEFLRK

mRNA and protein sequences for human lipocalin-2 (LCN2)

NM_005564 Homo sapiens lipocalin 2 (oncogene 24p3) (LCN2), mRNA [gi:5031852]

```
   1 atgcccctag gtctcctgtg gctgggccta gccctgttgg gggctctgca tgcccaggcc
  61 caggactcca cctcagacct gatcccagcc ccacctctga gcaaggtccc tctgcagcag
 121 aacttccagg acaaccaatt ccaggggaag tggtatgtgg taggcctggc agggaatgca
 181 attctcagag aagacaaaga cccgcaaaag atgtatgcca ccatctatga gctgaaagaa
 241 gacaagagct acaatgtcac ctccgtcctg tttaggaaaa agaagtgtga ctactggatc
 301 aggacttttg ttccaggttg ccagcccggc gagttcacgc tgggcaacat taagagttac
 361 cctggattaa cgagttacct cgtccgagtg gtgagcacca actacaacca gcatgctatg
 421 gtgttcttca agaaagtttc tcaaaacagg gagtacttca agatcaccct ctacgggaga
 481 accaaggagc tgacttcgga actaaaggag aacttcatcc gcttctccaa atatctgggc
 541 ctccctgaaa accacatcgt cttccctgtc ccaatcgacc agtgtatcga cggctga
```

Note: there is an additional 3' exon, not represented in the mRNA sequence above, that is included in the sequence that Affymetrix used in designing probes for LCN2 expression (and which was used in designing RT-PCR primers). The additional sequence is as follows:

```
   1 ggtgccgcca gctgccgcac cagcccgaac accattgagg gagctgggag accctcccca
  61 cagtgccacc catgcagctg ctccccaggc caccccgctg atggagcccc accttgtctg
 121 ctaaataaac atgtgc
```

Protein sequence for human lipocalin-1 (LCN2)

MPLGLLWLGLALLGALHAQAQDSTSDLIPAPPLSKVPLQQNFQD
NQFQGKWYVVGLAGNAILREDKDPQKMYATIYELKEDKSYNVTSVLFRKKKCDYWIRT
FVPGCQPGEFTLGNIKSYPGLTSYLVRVVSTNYNQHAMVFFKKVSQNREYFKITLYGR
TKELTSELKENFIRFSKYLGLPENHIVFPVPIDQCIDG

mRNA and protein sequences for human MMP-9

NM_004994 Homo sapiens matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase) (MMP9), mRNA [gi:482835]

1 agacacctct gccctcacca tgagcctctg gcagcccctg gtcctggtgc tcctggtgct
61 gggctgctgc tttgctgccc ccagacagcg ccagtccacc cttgtgctct tccctggaga
121 cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggtta
181 cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct
241 ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat
301 gcgaacccca cggtgcgggg tcccagacct gggcagattc caaacctttg agggcgacct
361 caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg
421 ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct
481 caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga
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601 tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa
661 gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttcccctt
721 catcttcgag ggccgctcct actctgcctg caccaccgac ggtcgctccg acggcttgcc
781 ctggtgcagt accacggcca actacgacac cgacgaccgg tttggcttct gccccagcga
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1441 tgtccacccc tcagagcgcc ccacagctgg ccccacaggt ccccctcag ctggccccac
1501 aggtcccccc actgctggcc cttctacggc cactactgtg cctttgagtc cggtggacga
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1681 ccttatcgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggtct ttgaggagcc
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1861 cggggccctc cggagtggca gggggaagat gctgctgttc agcgggcggc gcctctggag
1921 gttcgacgtg aaggcgcaga tggtggatcc ccggagcgcc agcgaggtgg accggatgtt
1981 ccccggggtg cctttggaca cgcacgacgt cttccagtac cgagagaaag cctatttctg
2041 ccaggaccgc ttctactggc gcgtgagttc ccggagtgag ttgaaccagg tggaccaagt
2101 gggctacgtg acctatgaca tcctgcagtg ccctgaggac tagggctccc gtcctgcttt
2161 gcagtgccat gtaaatcccc actgggacca accctgggga aggagccagt ttgccggata
2221 caaactggta ttctgttctg gaggaaaggg aggagtggag gtgggctggg ccctctcttc
2281 tcacctttgt tttttgttgg agtgtttcta ataaacttgg attctctaac cttt

Protein sequence for Homo sapien MMP9

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLFPGDLRTNLTDRQL
AEEYLYRYGYTRVAEMRGESKSLGPALLLLQKQLSLPETGELDSATLKAMRTPRCGVP
DLGRFQTFEGDLKWHHHNITYWIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVY
SRDADIVIQFGVAEHGDGYPFDGKDGLLAHAFPPGPGIQGDAHFDDDELWSLGKGVVV
PTRFGNADGAACHFPFIFEGRSYSACTTDGRSDGLPWCSTTANYDTDDRFGFCPSERL
YTRDGNADGKPCQFPFIFQGQSYSACTTDGRSDGYRWCATTANYDRDKLFGFCPTRAD
STVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGRLWCATTSNFDSDKKWGFCPDQG
YSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPPLHKDDVNGIRHLYGPRPEPE
PRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGPPTAGPSTATTVP
LSPVDDACNVNIFDAIAEIGNQLYLFKDGKYWRFSEGRGSRPQGPFLIADKWPALPRK
LDSVFEEPLSKKLFFFSGRQVWVYTGASVLGPRRLDKLGLGADVAQVTGALRSGRGKM
LLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYWRV
SSRSELNQVDQVGYVTYDILQCPED

mRNA and protein sequences for human CD24

L33930 Homo sapiens CD24 signal transducer mRNA, complete cds and 3' region [gi:500848]

```
   1 cggttctcca agcacccagc atcctgctag acgcgccgcg caccgacgga ggggacatgg
  61 gcagagcaat ggtggccagg ctggggctgg ggctgctgct gctggcactg ctcctaccca
 121 cgcagattta ttccagtgaa acaacaactg gaacttcaag taactcctcc cagagtactt
 181 ccaactctgg gttggcccca aatccaacta atgccaccac caaggcggct ggtggtgccc
 241 tgcagtcaac agccagtctc ttcgtggtct cactctctct tctgcatctc tactcttaag
 301 agactcaggc caagaaacgt cttctaaatt tccccatctt ctaaacccaa tccaaatggc
 361 gtctggaagt ccaatgtggc aaggaaaaac aggtcttcat cgaatctact aattccacac
 421 cttttattga cacagaaaat gttgagaatc ccaaatttga ttgatttgaa gaacatgtga
 481 gaggtttgac tagatgatga atgccaatat taaatctgct ggagtttcat gtacaagatg
 541 aaggagaggc aacatccaaa atagttaaga catgatttcc ttgaatgtgg cttgagaaat
 601 atggacactt aatactacct tgaaaataag aatagaaata aaggatggga ttgtggaatg
 661 gagattcagt tttcattggt tcattaattc tataaggcca taaaacaggt aatataaaaa
 721 gcttccatcg atctatttat atgtacatga gaaggaatcc ccaggtgtta ctgtaattcc
 781 tcaacgtatt gtttcgacgg cactaattta atgccgatat actctagatg aatgtttaca
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 901 ttgacattgc atttgacctt ttaggtagta attgacatgt gccagggcaa tgatgaatga
 961 gaatctaccc cagatccaag catcctgagc aactcttgat tatccatatt gagtcaaatg
1021 gtaggcattt cctatcacct gtttccattc aacaagagca ctacattctt ttagctaaac
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1561 gtatttggga agtgaagact ggaagctaat ttgcataaat tcacaaactt ttatactctt
1621 tctgtatata catttttttt ctttaaaaaa caactatgga tcagaatagc aacatttaga
1681 acacttttg ttatcagtca atatttttag atagttagaa cctggtccta agcctaaaag
1741 tgggcttgat tctgcagtaa atcttttaca actgcctcga cacacataaa ccttttaaa
1801 aatagacact ccccgaagtc ttttgtttgt atggtcacac actgatgctt agatgttcca
1861 gtaatctaat atggccacag tagtcttgat gaccaaagtc ctttttttcc atctttagaa
1921 aactacatgg gaacaaacag atcgaacagt tttgaagcta ctgtgtgtgt gaatgaacac
1981 tcttgcttta ttccagaatg ctgtacatct attttggatt gtatattgtg gttgtgtatt
2041 tacgctttga ttcatagtaa cttcttatgg aattgatttg cattgaacga caaactgtaa
2101 ataaaaagaa acggtg
```

Protein sequences for human CD24

MGRAMVARLGLGLLLLALLLPTQIYSSETTTGTSSNSSQSTSNS
GLAPNPTNATTKAAGGALQSTASLFVVSLSLLHLYS

Figure 12. (Page 1 of 33)

D30655. Homo sapiens mRNA...[gi:485387]:

Eukaryotic initiation factor 4AII

DNA sequence:

```
   1 gtggtttttc ggatcatgtc tggtggctcc gcggattata acagagaaca tggcggccca
  61 gagggaatgg accccgatgg tgtcatcgag agcaactgga atgagattgt tgataacttt
 121 gatgatatga atttaaagga gtctctcctt cgtggcatct atgcttacgg ttttgagaag
 181 ccttccgcta ttcagcagag agctattatt ccctgtatta aagggtatga tgtgattgct
 241 caagctcagt caggtactgg caagacagcc acatttgcta tttccatcct gcaacagttg
 301 gagattgagt tcaaggagac ccaagcacta gtattggccc ccaccagaga actggctcaa
 361 cagatccaaa aggtaattct ggcacttgga gactatatgg gagccacttg tcatgcctgc
 421 attggtggaa caaatgttcg aaatgaaatg caaaaactgc aggctgaagc accacatatt
 481 gttgttggta cacccgggag agtgtttgat atgttaaaca gaagatacct ttctccaaaa
 541 tggatcaaaa tgtttgtttt ggatgaagca gatgaaatgt tgagccgtgg ttttaaggat
 601 caaatctatg agattttcca aaaactaaac acaagtattc aggttgtgtt tgcttctgcc
 661 acaatgccaa ctgatgtgtt ggaagtgacc aaaaaattca tgagagatcc aattcgaatt
 721 ctggtgaaaa aggaagaatt gacccttgaa ggaatcaaac agttttatat taatgttgag
 781 agagaggaat ggaagttgga tacactttgt gacttgtacg agacactgac cattacacag
 841 gctgttattt ttctcaatac gaggcgcaag gtggactggc tgactgagaa gatgcatgcc
 901 agagacttca cagtttctgc tctgcatggt gacatggacc agaaggagag agatgttatc
 961 atgagggaat tccggtcagg gtcaagtcgt gttctgatca ctactgactt gttggctcgc
1021 gggattgatg tgcaacaagt gtctttggtt ataaattatg atctacctac caatcgtgaa
1081 aactatattc acagaattgg cagaggggt cgatttggga ggaaaggtgt ggctataaac
1141 tttgttactg aagaagacaa gaggattctt cgtgacattg agactttcta caatactaca
1201 gtggaggaga tgcccatgaa tgtggctgac cttatttaat tcctgggatg agagttttgg
1261 atgcagtgct cgctgttgct gaataggcga tcacaacgtg cattgtgctt ctttctttgg
1321 gaatatttga atcttgtctc aatgctcata acggatcaga aatacagatt ttgatagcaa
1381 agcgacgtta gtcgtgagct cttgtgagga aagtcattgg ctttatcctc tttagagtta
1441 gactgttggg gtgggtataa aagatggggt ctgtaaaatc tttctttctt agaaatttat
1501 ttcctagttc tgtagaaatg gttgtattag atgttctcta tcatttaata atatacttgt
1561 ggactaaaag atataagtgc tgtataaaat cagccaatta tgttaaacta gcatatctgc
1621 ctttattgtg tttgtcatta gcctgagtag aaaggccttt aaaatttttt tagaaagcat
1681 ttgaatgcat tttgtttggt attgtattta ttcaataaag tatttaatta gtgctaagtg
1741 tgaactggac cctgttgcta agccccagca agcaatccta ggtagggttt aatccccagt
1801 aaaattgcca tattgcacat gtcttaatga agtttgaatg ttaaataaat tgtatattca
1861 cttt
```

protein sequence:

```
MSGGSADYNREHGGPEGMDPDGVIESNWNEIVDNFDDMNLKESLLRGIYAYGFEKPSAIQQRAIIPCIKGYDVIAQAQ
SGTGKTATFAISILQQLEIEFKETQALVLAPTRELAQQIQKVILALGDYMGATCHACIGGTNVRNEMQKLQAEAPHIVVG
TPGRVFDMLNRRYLSPKWIKMFVLDEADEMLSRGFKDQIYEIFQKLNTSIQVVFASATMPTDVLEVTKKFMRDPIRILV
KKEELTLEGIKQFYINVEREEWKLDTLCDLYETLTITQAVIFLNTRRKVDWLTEKMHARDFTVSALHGDMDQKERDVIM
REFRSGSSRVLITTDLLARGIDVQQVSLVINYDLPTNRENYIHRIGRGGRFGRKGVAINFVTEEDKRILRDIETFYNTTVE
EMPMNVADLI
```

Figure 12. (Page 2 of 33)

M92383. Homo sapiens thym...[gi:339696]:

Homo sapiens thymosin beta-10 gene

DNA sequence:

1 cgtcctacat ctcgcgcata cacgcccacg tgcgcacatc actgggggtg ccncgggaga
61 cagagccgct ggtagcctaa ggnggggggg cagccaggag aaagccccgc cgctgctcgt
121 cccgcccctc gggtgccagc accgcccctg ctgcggcggg tgaggggcgg ggcggggccg
181 cggcgtatat aaggctaggc ggggcgccgc tcttttgttt cttgctgcag caacgcgagt
241 gggagcacca ggatctcggg ctcggaacga gactgcacgg tgacgtgacg gccgggcggg
301 ggcccagggt gtggtcggat ccggtgcacc gcgggcgcgc aacccggaca ggcgcttctc
361 ggaccggacg caggggccgc gaccacgccc tgggaccgag aagaggggtg cggacgcgcc
421 cagatcctcg gccttggggc tgctcggcag ccttggcgcg agtgccacgt cgagaggcgt
481 cggcggggag cgcggaaggg gacggcctgc gcccaggccc aggtcaagcg ccttggtttg
541 cccactagga ttgttttaag aaaatggcag acaaaccaga catgggggaa atcgccagct
601 tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag
661 agagtgagtg tgcctcggtc tccgcgcccc agcccagccc ctcaccctgc tcttccttgc
721 aaacccactc ctccaccccc caccccgccg ttgtccccgg tgtgggcggc cccggcactc
781 tttcagtttc acaaagcgcc ttgtttctcc ccagccccaa gcttccttct aaatcccaca
841 cctcgtggtg ctcatcacac cgggaagcac ctcggttgcg ggtggggggt tgcagcnccc
901 ctccagcgcc ccgttccgtc tcaagccatt gagcaggaga agcggagtga aatttcctaa
961 gatcctggag gatttcctac cccccgtctc tcggagcacc ccagtcgctg atgtggagaa
1021 gagccaccct gcaagatgga cacgagtcca caagctgcac tgtgaacctg cgagcccgcg
1081 ccgatgccac cggcctgtgg tcgtctgaag ggaccccccc ccaatcggac tgccaaattc
1141 tcggtttgcc ccgggatatt atagaaaatt atttgtatga ataatgaaaa taaaacacac
1201 ctcgttggca tggctggcgg tggtctgagt gttttagtta gtatgggtgc agtccactgc
1261 ag

protein sequence:

DCFKKMADKPDMGEIASFDKAKLKKTETQEKNTLPTKETIEQEKRSEIS

Figure 12. (Page 3 of 33)

X79536. H.sapiens mRNA fo...[gi:496897]:

H.sapiens mRNA for hnRNPcore protein A1

DNA sequence:

1 ttaaagtctc tcttcaccct gccgtcatgt ctaagtcaga gtctcctaaa gagcccgaac
61 agctgaggaa gctcttcatt ggagggttga gctttgaaac aactgatgag agcctgagga
121 gccattttga gcaatgggga acgctcacgg actgtgtggt aatgagagat ccaaacacca
181 agcgctctag gggctttggg tttgtcacat atgccactgt ggaggaggtg gatgcagcta
241 tgaatgcaag gccacacaag gtggatggaa gagttgtgga accaaagaga gctgtctcca
301 gagaagattc tcaaagacca ggtgcccact taactgtgaa aaagatattt gttggtggca
361 ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg
421 aagtgattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gcctttgtaa
481 cctttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtgaatg
541 gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca
601 gccaaagagg tcgaagtggt tctggaaact ttggtggtgg tcgtggaggt ggtttcggtg
661 ggaatgacaa cttcggtcgt ggaggaaact tcagtggtcg tggtggcttt ggtggcagcc
721 gtggtggtgg tggatatggt ggcagtgggg atggctataa tggatttggc aatgatggaa
781 gcaattttgg aggtggtgga agctacaatg attttgggaa ttacaacaat cagtcttcaa
841 attttggacc catgaaggga ggaaattttg gaggcagaag ctctggcccc tatggcggtg
901 gaggccaata ctttgcaaaa ccacgaaacc aaggtggcta tggcggttcc agcagcagca
961 gtagctatgg cagtggcaga agattttaat tagggaggag tctgctacta gtcttatcag
1021 ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ccttgtgaag
1081 acctttatct gagccactgt acttcgttat cacgccatgc agtttacatg agctgttctg
1141 cagctcgaaa ttccattttg tgaatgggtt tttttttta ataaactgta tttaactt

protein sequence:

MSKSESPKEPEQLRKLFIGGLSFETTDESLRSHFEQWGTLTDCVVMRDPNTKRSRGFGFVTYATVEEVDAAMNARP
HKVDGRVVEPKRAVSREDSQRPGAHLTVKKIFVGGIKEDTEEHHLRDYFEQYGKIEVIEIMTDRGSGKKRGFAFVTFD
DHDSVDKIVIQKYHTVNGHNCEVRKALSKQEMASASSSQRGRSGSGNFGGGRGGGFGGNDNFGRGGNFSGRGGF
GGSRGGGGYGGSGDGYNGFGNDGSNFGGGGSYNDFGNYNNQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKP
RNQGGYGGSSSSSSYGSGRRF

Figure 12. (Page 4 of 33)

X14046. Human mRNA for le...[gi:29793]:

Human mRNA for leukocyte antigen CD37

DNA sequence:

```
   1 gtctccccca ctgtcagcac ctcttctgtg tggtgagtgg accgcttacc ccactaggtg
  61 aagatgtcag cccaggagag ctgcctcagc ctcatcaagt acttcctctt cgttttcaac
 121 ctcttcttct tcgtcctcgg cagcctgatc ttctgcttcg gcatctggat cctcatcgac
 181 aagaccagct tcgtgtcctt tgtgggcttg gccttcgtgc ctctgcagat ctggtccaaa
 241 gtcctggcca tctcaggaat cttcaccatg ggcatcgccc tcctgggttg tgtgggggcc
 301 ctcaaggagc tccgctgcct cctgggcctg tattttggga tgctgctgct cctgtttgcc
 361 acacagatca ccctgggaat cctcatctcc actcagcggg cccagctgga gcgaagcttg
 421 cgggacgtcg tagagaaaac catccaaaag tacggcacca accccgagga gaccgcggcc
 481 gaggagagct gggactatgt gcagttccag ctgcgctgct gcggctggca ctacccgcag
 541 gactggttcc aagtcctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc
 601 tcctgctaca acttgtcggc gaccaacgac tccacaatcc tagataaggt gatcttgccc
 661 cagctcagca ggcttggaca cctggcgcgg tccagacaca gtgcagacat ctgcgctgtc
 721 cctgcagaga gccacatcta ccgcgagggc tgcgcgcagg gcctccagaa gtggctgcac
 781 aacaacctta tttccatagt gggcatttgc ctgggcgtcg gcctactcga gctcgggttc
 841 atgacgctct cgatattcct gtgcagaaac ctggaccacg tctacaaccg gctcgctcga
 901 taccgttagg ccccgccctc cccaaagtcc cgccccgccc ccgtcacgtg cgctgggcac
 961 ttccctgctg cctgtaaata tttgtttaat ccccagttcg cctggagccc tccgccttca
1021 cattcccctg gggacccacg tggctgcgtg cccctgctgc tgtcacctct cccacgggac
1081 ctggggcttt cgtccacagc ttcctgtccc catctgtcgg cctac
```

protein sequence:

```
MSAQESCLSLIKYFLFVFNLFFFVLGSLIFCFGIWILIDKTSFVSFVGLAFVPLQIWSKVLAISGIFTMGIALLGCVGALKEL
RCLLGLYFGMLLLLFATQITLGILISTQRAQLERSLRDVVEKTIQKYGTNPEETAAEESWDYVQFQLRCCGWHYPQDW
FQVLILRGNGSEAHRVPCSCYNLSATNDSTILDKVILPQLSRLGHLARSRHSADICAVPAESHIYREGCAQGLQKWLHN
NLISIVGICLGVGLLELGFMTLSIFLCRNLDHVYNRLARYR
```

Figure 12. (Page 5 of 33)

M32578. Human MHC class I...[gi:188305]:

Human MHC class II HLA-DR beta-1

DNA sequence:

1 agttctccct gagtgagact tgcctgctcc tctggcccct ggtcctgtcc tgttctccag
61 catggtgtgt ctgaagctcc ctggaggttc ctacatggca gtgctgacag tgacactgat
121 ggtgctgagc tccccactgg ctttggctgg ggacacccga ccatgtttct tgcagcagga
181 taagtatgag tgtcatttct tcaacgggac ggagcgggtg cggttcctgc acagaggcat
241 ctataaccaa caggagaacg tgcgcttcga cagcgacgtg ggggagtacc gggcggtgac
301 ggagctgggg cggcctgacg ctgagtactg gaacagccag aaggacatcc tggagcaggc
361 gcgggccgcg gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt
421 gcagcggcga gttgagccta aggtgactgt gtatcctgca aggacccaga ccctgcagca
481 ccacaacctc ctggtctgct ctgtgaatgg tttctatcca ggcagcattg aagtcaggtg
541 gttccggaac ggccaggaag agaaggctgg ggtggtgtcc acaggcctga ttcagaatgg
601 agactggacc ttccagattc tggtgatgct ggaaacagtt cctcggagtg gagaggttta
661 cacctgccaa gtggagcacc caagcgtgac gagccctctc acagtggaat ggagagcaca
721 gtctgaatct gcacagagca agatgctgag tggaatcggg ggctttgtgc tgggcctgct
781 cttccttggg gccgggctat tcatctactt caagaatcag aaagggcact ctggacttca
841 cccaacagga ctcgtgagct gaagtgcaga tgaccacatt caaggggaa ccttctgccc
901 cagctttgca tgatgaaaag ctttcctgct tggctcttat tcttccacaa gagaggactt
961 tctcaggccc tggttgctac cggttcagca actctgcaga aaatgtccat ccttgtggct
1021 tcctcagctc ctgcccttgg cctgaagtcc cagcattgat ggcagtgcct catcttcaac
1081 tttagtgctc ccctttacct aaccctacgg cctcccatgc atctgtactc cccctgtgcc
1141 acaaatggac tacgttatta aatttttctg aagcccagag ttaaaaatca tctgtccacc
1201 tggcaccaaa gacaaa

protein sequence:

MVCLKLPGGSYMAVLTVTLMVLSSPLALAGDTRPCFLQQDKYECHFFNGTERVRFLHRGIYNQQENVRFDSDVGEY
RAVTELGRPDAEYWNSQKDILEQARAAVDTYCRHNYGAVESFTVQRRVEPKVTVYPARTQTLQHHNLLVCSVNGFY
PGSIEVRWFRNGQEEKAGVVSTGLIQNGDWTFQILVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRAQSESAQSKM
LSGIGGFVLGLLFLGAGLFIYFKNQKGHSGLHPTGLVS

Figure 12. (Page 6 of 33)

U54558. Homo sapiens tran...[gi:2351377]:

Homo sapiens translation initiation factor eIF3 p66 subunit mRNA

DNA sequence:

1 gaattcggca cgagctaacg cggtccccgg cacgcaccat ctgttgccat cccggccggc
61 cgaggccatt gcagattttg gaagatggca aagttcatga cacccgtgat ccaggacaac
121 ccctcaggct ggggtccctg tgcggttccc gagcagtttc gggatatgcc ctaccagccg
181 ttcagcaaag gagatcggct aggaaaggtt gcagactgga caggagccac ataccaagat
241 aagaggtaca caaataagta ctcctctcag tttggtggtg gaagtcaata tgcttatttc
301 catgaggagg atgaaagtag cttccagctg gtggatacag cgcgcacaca gaagacggcc
361 taccagcgga atcgaatgag atttgcccag aggaacctcc gcagagacaa agatcgtcgg
421 aacatgttgc agttcaacct gcagatcctg cctaagagtg ccaaacagaa agagagagaa
481 cgcattcgac tgcagaaaaa gttccagaaa caatttgggg ttaggcagaa atgggatcag
541 aaatcacaga aaccccgaga ctcttcagtt gaagttcgta gtgattggga agtgaaagag
601 gaaatggatt ttcctcagtt gatgaagatg cgctacttgg aagtatcaga gccacaggac
661 attgagtgtt gtggggccct agaatactac gacaaagcct ttgaccgcat caccacgagg
721 agtgagaagc cactgcggag catcaagcgc atcttccaca ctgtcaccac cacagacgac
781 cctgtcatcc gcaagctggc aaaaactcag gggaatgtgt ttgccactga tgccatcctg
841 gccacgctga tgagctgtac ccgctcagtg tattcctggg atattgtcgt ccagagagtt
901 gggtccaaac tcttctttga caagagagac aactctgact ttgacctcct gacagtgagt
961 gagactgcca atgagccccc tcaagatgaa ggtaattcct tcaattcacc ccgcaacctg
1021 gccatggagg caacctacat caaccacaat ttctcccagc agtgcttgag aatggggaag
1081 gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa
1141 atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt
1201 gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac
1261 atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag
1321 ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg
1381 gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg
1441 tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag
1501 cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgggg cattttacgc
1561 tgcgtcattg acatctgcat gaagctggag gagggcaaat acctcatcct caaggacccc
1621 aacaagcagg tcatccgtgt ctacagcctc cctgatggca ccttcagctc tgatgaagat
1681 gaggaggaag aggaggagga agaagaggaa gaagaagagg aagaaactta aaccagtgat
1741 gtggagctgg agtttgtcct tccaccgaga ctacgagggc ctttgatgct tagtggaatg
1801 tgtgtctaac ttgctctctg acatttagca gatgaaataa aatatatatc tgtttagtct
1861 tttaaaaaaa aaaaaaaaaa a

Protein sequence:

MAKFMTPVIQDNPSGWGPCAVPEQFRDMPYQPFSKGDRLGKVADWTGATYQDKRYTNKYSSQFGGGSQYAYFHE
EDESSFQLVDTARTQKTAYQRNRMRFAQRNLRRDKDRRNMLQFNLQILPKSAKQKERERIRLQKKFQKQFGVRQKW
DQKSQKPRDSSVEVRSDWEVKEEMDFPQLMKMRYLEVSEPQDIECCGALEYYDKAFDRITTRSEKPLRSIKRIFHTVT
TTDDPVIRKLAKTQGNVFATDAILATLMSCTRSVYSWDIVVQRVGSKLFFDKRDNSDFDLLTVSETANEPPQDEGNSF
NSPRNLAMEATYINHNFSQQCLRMGKERYNFPNPNPFVEDDMDKNEIASVAYRYRRWKLGDDIDLIVRCEHDGVMT
GANGEVSFINIKTLNEWDSRHCNGVDWRQKLDSQRGAVIATELKNNSYKLARWTCCALLAGSEYLKLGYVSRYHVKD
SSRHVILGTQQFKPNEFASQINLSVENAWGILRCVIDICMKLEEGKYLILKDPNKQVIRVYSLPDGTFSSDEDEEEEEEE
EEEEEEEET

Figure 12. (Page 7 of 33)

X58965. H.sapiens RNA for...[gi:35069]:

H.sapiens RNA for nm23-H2 gene

DNA sequence:

```
   1 cggccacgag gcggaatccc ttctgctctc ccagcgcagc gccgccgccc ggcccctcca
  61 gcttcccgga ccatggccaa cctggagcgc accttcatcg ccatcaagcc ggacggcgtg
 121 cagcgcggcc tggtgggcga gatcatcaag cgcttcgagc agaagggatt ccgcctcgtg
 181 gccatgaagt tcctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa
 241 gaccgaccat tcttccctgg gctggtgaag tacatgaact cagggccggt tgtggccatg
 301 gtctgggagg ggctgaacgt ggtgaagaca ggccgagtga tgcttgggga gaccaatcca
 361 gcagattcaa agccaggcac cattcgtggg gacttctgca ttcaggttgg caggaacatc
 421 attcatggca gtgattcagt aaaaagtgct gaaaaagaaa tcagcctatg gtttaagcct
 481 gaagaactgg ttgactacaa gtcttgtgct catgactggg tctatgaata agaggtggac
 541 acaacagcag tctccttcag cacggcgtgg tgtgtccctg gacacagctc ttcattccat
 601 tgacttagag gcaacaggat tgatcattct tttatagagc atatttgcca ataaagcttt
 661 tggaagccgg
```

protein sequence:

MANLERTFIAIKPDGVQRGLVGEIIKRFEQKGFRLVAMKFLRASEEHLKQHYIDLKDRPFFPGLVKYMNSGPVVAMVW
EGLNVVKTGRVMLGETNPADSKPGTIRGDFCIQVGRNIIHGSDSVKSAEKEISLWFKPEELVDYKSCAHDWVYE

Figure 12. (Page 8 of 33)

M17885. Human acidic ribo...[gi:190231]:

Human acidic ribosomal phosphoprotein P0 mRNA

DNA sequence:

```
   1 cttctctcgc caggcgtcct cgtggaagtg acatcgtctt taaacccccc cgtggcaatc
  61 cctgacgcac cgccgtgatg cccagggaag acagggcgac ctggaagtcc aactacttcc
 121 ttaagatcat ccaactattg gatgattatc cgaaatgttt cattgtggga gcagacaatg
 181 tgggctccaa gcagatgcag cagatccgca tgtcccttcg cgggaaggct gtggtgctga
 241 tgggcaagaa caccatgatg cgcaaggcca tccgagggca cctggaaaac aacccagctc
 301 tggagaaact gctgcctcat atccgggggа atgtgggctt tgtgttcacc aaggaggacc
 361 tcactgagat cagggacatg ttgctggcca ataaggtgcc agctgctgcc cgtgctggtg
 421 ccattgcccc atgtgaagtc actgtgccag cccagaacac tggtctcggg cccgagaaga
 481 cctccttttt ccaggcttta ggtatcacca ctaaaatctc caggggcacc attgaaatcc
 541 tgagtgatgt gcagctgatc aagactggag acaaagtggg agccagcgaa gccacgctgc
 601 tgaacatgct caacatctcc cccttctcct ttgggctggt catccagcag gtgttcgaca
 661 atggcagcat ctacaaccct gaagtgcttg atatcacaga ggaaactctg cattctcgct
 721 tcctggaggg tgtccgcaat gttgccagtg tctgtctgca gattggctac ccaactgttg
 781 catcagtacc ccattctatc atcaacgggt acaaacgagt cctggccttg tctgtggaga
 841 cggattacac cttcccactt gctgaaaagg tcaaggcctt cttggctgat ccatctgcct
 901 ttgtggctgc tgcccctgtg gctgctgcca ccacagctgc tcctgctgct gctgcagccc
 961 cagctaaggt tgaagccaag gaagagtcgg aggagtcgga cgaggatatg ggatttggtc
1021 tctttgacta atcaccaaaa agcaaccaac ttagccagtt ttatttgcaa aacaaggaaa
1081 taaaggctta cttcttt
```

protein sequence:

```
MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGKAVVLMGKNTMMRKAIRGHLENNPALEK
LLPHIRGNVGFVFTKEDLTEIRDMLLANKVPAAARAGAIAPCEVTVPAQNTGLGPEKTSFFQALGITTKISRGTIEILSDV
QLIKTGDKVGASEATLLNMLNISPFSFGLVIQQVFDNGSIYNPEVLDITEETLHSRFLEGVRNVASVCLQIGYPTVASVP
HSIINGYKRVLALSVETDYTFPLAEKVKAFLADPSAFVAAAPVAAATTAAPAAAAAPAKVEAKEESEESDEDMGFGLFD
```

Figure 12. (Page 9 of 33)

X52851. Human cyclophilin...[gi:30167]:

Human cyclophilin gene for cyclophilin

DNA sequence:

1 gaattccctt gtaaggtttt cttaacaaaa caccagtcac ataagtgcat tttattttat
61 atttttgttt atttatttga gacggagtct cttgtctctc aggctggagt gcagtggcgc
121 catctctgct cgctgcaacc tccacctcct gggttccagc gattctcctg cctcagcctc
181 ccgagggggt agctgggact acaggtgcgc accaccatgc ccagctaatt ttgtattttt
241 cgtagagatg gggtttcacc atgttgtcca ggctggtctt gaactcctga cctcaggtga
301 tcctcccgcc tcggcctccc aaagtgctgg aattacaggc gtgatccacc gcacccggcc
361 tatttttttga gagagggtca cactctgtcg tcccggctgg aatgcagtga tgcgatcacc
421 gcccactaca gcctcgacct ccgggctcaa gcaatcctcc ccgcccagcc tcctgagtag
481 cgagcgcctc gacgcccagc taatttttat ttttatttat ttttttgtag agacggcgtc
541 tctctaagat gcccaggctg gtggccggtg tcgaactcct aagatgaagc gatcctcccc
601 ggccttggcc tccgcgcctc ctaaagcgcc aggtatgagc caccgcgcct ggcctacaag
661 tgcattttaa ttaaagtatt attaatgtct ttgcctgaag aaattcgctt ttaaattgtg
721 acttatcttt cacccaaaaa tcaaagcaca attcagcccc gaggcggggg cggtaggagc
781 tgggcggggc gggggcaggg aaagaccagg agcagagatt caaaaagagt aagagggcaa
841 aatgtgcata atgcatcttc acaggtaaga gcctggccag gctcctgttt taatggcttc
901 ctcctgaaga agattcaagc agagtgtaag atattttcgg aaagtagagc attttgaaag
961 catttcataa tctctcaaaa ccggagactg ctcctgtccc acctcgttag agaaaacagc
1021 gatgctcaaa ggcaacctcc ttcctgacat tgcctggtag gacgcgacgt ggtgtttgcc
1081 cgcgcggaat gcggacgcaa ggctgctcct aggtctcggg gacgcgccat ccccatttcc
1141 gctcgcggag gcgtagggtc cgggcgcggg accccagtcg accttgactg gcggcgcgac
1201 cttgaggcct gcgttcgcct cagttgcccc ctctgtgcaa tggggagacg cgcctcatcg
1261 cttgacaacg gccgaagagc cgccgcgctt ccgtctcccg cgtgcgcgcg ccatgctgcc
1321 caccccgtt ccgcactgac cctcccccgt gccccgcgtc ccgtactgcc gccccgcccc
1381 gagtcccatg ccgcagccac cgcgacggag cccgcaggcg ggaacctgcc tccgcgcgtt
1441 agcgcgcacg cgcgcctcat gtgtcgtccc catcagcgcc ggcttccgtc tataggccag
1501 atgcactgtc actctggcga agtcgcagac ccgattggcc gggacggagg cgcgagaccg
1561 ggttgcgggc ggggccgaac gtggtataaa acgggcggga ggccaggctc gtgccgtttt
1621 gcagacgcca ccgccgagga aaaccgtgta ctattagcca tggtcaaccc caccgtgttc
1681 ttcgacattg ccgtcgacgg cgagcccttg ggccgcgtct cctttgaggt cgggcgggcg
1741 gcggcgtgcg ggaatggggc ccagaaagtg ggccggggtc ggggtgggtg gtagcgcccc
1801 aaaggcccgg gcgcggggcg accctgcttg aggggcgagc gcgggcgggc tgcggcgcca
1861 tttcctgacg aggggccatt ttgggaggtc cgcgagtcgc gggaggaggc cgggacgcgg
1921 cggacaaagg caggcggggc ggctgcgagg ccgttggggg agggggcccg cgtccgcccg
1981 cccgcctcat gtggccgcgc cctgtcctgt ccgacgcacg tgctcggcgg ccgcgctcag
2041 gtccgcgcct tgagagtcgt tgtccgccct agcttggcct gggcgccgca gaccggagcc
2101 agaagcacgc tcgcgggggc ttgcgaccgc cttcctggga agctgtcccc tggcaggcat
2161 gggtgcttta catcctgagc tgggaagctg tttgcttgag ggtttttctc aaggatcgag
2221 gcgcggtgtg agcccgtcca tgctcggtcc tgtagatccc gggaggccat gttataaaag
2281 gagacttgct gggatgtgac gggttgccac ttgaaatatc ttccatttgg ataaagtagg
2341 aatatttata catgtgcccc aaacgtccct ccgtgtcccc caccccaag cggaaatgtg
2401 aaaatgggcc ttgcctttgc tggtgcccaa ggaccgcctt ccactgcagt gacggcgctg
2461 gcgggggagg cgctcttgag cccctcccga ttgtccctct gcctagcaag caagttgcga
2521 ctggccacaa ggcaggcctc ttccgaccaa ggtggattac cagtgattac ctaattagtt
2581 ttgagagcgt taaatgagtt cttaaagatc agttgtaatt atagcatagt atctaaactt
2641 ggcgcgtgtc ttcaaagtta aatattgagt acgattccgt tccagttaac atggatagac
2701 cttagggagt agcgaaatag gatgttagtg gttttattcc tttaaatcac atctcaaaag

Figure 12. (Page 10 of 33)

2761 gccaccaatg gctagtttgg atcttattcc gaaaatagat tgatcctcat gcagtcttcg
2821 tgaggacaga gcgatttcct tgttgcctac cctgtccata gtgcctggca cataggcact
2881 gaaacactgc atgttaatcc acaccccacc ccacctatga gtgtagtcaa agctggtaag
2941 tgacaagggc tttcgtggaa acttggcctg acctaatgtt gggcatcagg ttacccaaag
3001 agcttcaggg aaatgagaaa ggacttgcag gtcttgatga gaatggaggg gtaactgcca
3061 atgagggctt tggctttagc gaaagtctga aagggaagcc ataggaactt aaacgtaccg
3121 actataaagc tctgagaaaa gctgatgttt tagaaagacc atacattcta ggtacaaata
3181 cctaaaaact aaaaaataag tacgttggcc aggcgggcgg atcacgaagt caggagattg
3241 agaccatcct gggcccctgg tgaaacccca cctctattaa aaatacaaaa attagctggg
3301 cgtggtggcg cttgcctgta atctcagcta ctctagaggc tgaggcagga gatcgcttga
3361 accccggagg cggaggctgc agtgagccga gatcgtgcca ctgcactcca gcctggtgac
3421 agcgagactc ttgtctcaaa aaaaaaaaag tacattgcta taagagaagt gcacacggat
3481 actagtagtt aattcagtca catctgtgaa atagcttata aaatgctact tttaaacaag
3541 ctgtttttat gaaagggctt gtaaatgttt atggtattta agctacctct ctagccataa
3601 cgtattatac attcaagaaa ggttcaaaac cagatatact agaaaccaat ctttatttt
3661 taccccacta ctaggtaagg gcctggatac caagaagtga ctgctcatct aatccataaa
3721 gctatgttaa cagattggag gtagtagcat tttcattaca agtgactaaa agaacagctg
3781 tttacccctg atcgtgcagc agtgcttgct gttccttaga attttgcctt gtaagttcta
3841 gctcaagttg gggggtggtg atagacattt aagaagccat atatcttttc agaagtaggt
3901 gtgatgtact aaaagtttga gacactttct agaagtctca ctatttaagt tatgactagt
3961 attggatttt tggcatgtct ttgggtttca tgtttcttaa cccaactgcc tgcagggcct
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4081 gaaaatgaat ttatgactca gaagccccta aagacatggg tactaagcaa caaaataagc
4141 agatgttaat taactgtaat tttctcttac agctgtttgc agacaaggtc ccaaagacag
4201 caggttggtc cattttctaa gtttaacaaa gatgttccaa ttgtgacagt ttgtgtgtgt
4261 gtgtgtatat atatattttt atgtatgtat atatgtgttt aatttttttt taaacagaaa
4321 attttcgtgc tctgagcact ggagagaaag gatttggtta taagggttcc tgctttcaca
4381 gaattattcc agggtttatg tgtcaggtac gaaatttact gaattttatt ttatttgggt
4441 tgctcccttc atttgggatt gagccagaat atttcaggat acacatatct gaactgttac
4501 tctaccattt cggttctatt taacccttct attcagtttg aacttgggtt taaagtttga
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4681 gaaatttgaa gatgagaact tcatcctaaa gcatacgggt cctggcatct tgtccatggc
4741 aaatgctgga cccaacacaa atggttccca gtttttcatc tgcactgcca agactgagtg
4801 gtaagggtac aacatggcac actaaccacc tgactaaatg aaaagttgcc ctgggggggaa
4861 cggaacaaac actacttttc ttcaaccttt gcttccacag acttttttcat ccctaagata
4921 ctagaagaag agcatacata aatgacaaat atagccaatg tgatacagaa tgtcagatac
4981 tatgatagaa acttggccct tagctgggtg gttgaattag gtgctacttt tttgagatgg
5041 agttttgctc tgttgccagg ttggagtgca gtggcacaat ctgggctcac tgcaacctct
5101 gcctcctggg ttcaagcgat tctcctgcct tggcctcctg agtagctgag aatacagatg
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5221 gccaagctgg tcttgaactc gtgacttaag gtgaaccacc tgccttggcc ccccaaagtg
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5341 cttttctcag actggatctc gctcttatct cccaggttgg agtgcagtgg tgccatctca
5401 gctcactgca acctcctccc gggttcaagc aattcttctg cctcagcctc tcaagtagct
5461 ggaactacag gcatgcacca ccactcccag ctaaattgtg tattattagt agagcgggat
5521 ttaccatgtt gtccaggctg gtctcgaact cctgggctca agtgatctgc ctgccttgac
5581 ccccccgaag tgctgggatt acaggcatga gccactgtgc ccacccaatt aagtgctgct
5641 tttatgttac tattaataac atgcggttgg ttgggttttt tgtttctttg gggtttttgt
5701 tttgttttgt ttgtttttgg gggaggggggg cgcaattcat tctatatgtg taactctttt
5761 ttgagatgga gtttcgctct gtcgcccagg ctggagtgca gtggcgcgat ctcggctcac

Figure 12. (Page 11 of 33)

5821 tgcaagctcc gcctcccagg ttcacgccat tctcctgcct cagcctcccg agtagctggg
5881 actataggca catgccacca tgcccggcta atttttgta tttttagtag agacagggtt
5941 tcaccgtgtt agccaggatg gtctcgatct cctgacctcg tgatccgccc gccttggcct
6001 cccaaagtgc tgggattaca ggcgtgagcc accgcacccg gcctatatgt gtaactcttt
6061 aatggtaatt ggagaatcat gtttaatgac atttagtaca aaaggcttca gttaaaaaaa
6121 aaaaaaaaaa gctacctttc tcgtcttggt tcatgacaca tggaggctgc ttgtttgtgg
6181 ttgccagtca taatgattgt tcttcctttt caaggttgga tggcaagcat gtggtgtttg
6241 gcaaagtgaa agaaggcatg aatattgtgg aggccatgga gcgctttggg tccaggaatg
6301 gcaagaccag caagaagatc accattgctg actgtggaca actcgaataa gtttgacttg
6361 tgttttatct taaccaccag atcattcctt ctgtagctca ggagagcacc cctccacccc
6421 atttgctcgc agtatcctag aatctttgtg ctctcgctgc agttcccttt gggttccatg
6481 ttttccttgt tccctcccat gcctagctgg attgcagagt taagtttatg attatgaaat
6541 aaaaactaaa taacaattgt cctcgtttga gttaagtgtt gatgtaggct ttattttaag
6601 cagtaatggg ttacttctga aacatcactt gtttgcttaa ttctacacag tacttagatt
6661 ttttttactt tccagtccca ggaagtgtca atgtttgttg agtggaatat t

protein sequence for Human cyclophilin gene for cyclophilin:
MVNPTVFFDIAVDGEPLGRVSFELFADKVPKTAENFRALSTGEKGFGYKGSCFHRIIPGFMCQGGDFTRHNGTGGKSI
YGEKFEDENFILKHTGPGILSMANAGPNTNGSQFFICTAKTEWLDGKHVVFGKVKEGMNIVEAMERFGSRNGKTSKKI
TIADCGQLE

Figure 12. (Page 12 of 33)

M12886. Human T-cell rece...[gi:339009]:

Human T-cell receptor active beta-chain mRNA

DNA sequence:

```
   1 gtgtgaggcc atcacggaag atgctgctgc ttctgctgct tctggggcta gcaggctccg
  61 ggcttggtgc tgtcgtctct caacatccga gctgggttat ctgtaagagt ggaacctctg
 121 tgaagatcga gtgccgttcc ctggactttc aggccacaac tatgttttgg tatcgtcagt
 181 tcccgaaaca gagtctcatg ctgatggcaa cttccaatga gggctccaag gccacatacg
 241 agcaaggcgt cgagaaggac aagtttctca tcaaccatgc aagcctgacc ttgtccactc
 301 tgacagtgac cagtgcccat cctgaagaca gcagcttcta catctgcagt gctagagagt
 361 cgactagcga tccaaaaaat gagcagttct tcgggccagg gacacggctc accgtgctag
 421 aggacctgaa aaacgtgttc ccacccgagg tcgctgtgtt tgagccatca gaagcagaga
 481 tctcccacac ccaaaaggcc acactggtgt gcctggccac aggcttctac cccgaccacg
 541 tggagctgag ctggtgggtg aatgggaagg aggtgcacag tggggtcagc acagacccgc
 601 agcccctcaa ggagcagccc gccctcaatg actccagata ctgcctgagc agccgcctga
 661 gggtctcggc caccttctgg cagaaccccc gcaaccactt ccgctgtcaa gtccagttct
 721 acgggctctc ggagaatgac gagtggaccc aggatagggc caaacctgtc acccagatcg
 781 tcagcgccga ggcctggggt agagcagact gtggcttcac ctccgagtct taccagcaag
 841 gggtcctgtc tgccaccatc ctctatgaga tcttgctagg gaaggccacc ttgtatgccg
 901 tgctggtcag tgccctcgtg ctgatggcca tggtcaagag aaaggattcc agaggctagc
 961 tccaaaacca tcccaggtca ttcttcatcc tcacccagga ttctcctgta cctgctccca
1021 atctgtgttc ctaaaagtga ttctcactct gcttctcatc tcctacttac atgaatactt
1081 ctctcttttt tctgtttccc tgaagattga gctccc
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protein sequence:

MLLLLLLLGLAGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGV
EKDKFLINHASLTLSTLTVTSAHPEDSSFYICSARESTSDPKNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHT
QKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQ
FYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDS
RG

Figure 12. (Page 13 of 33)

M83664. Human MHC class I...[gi:188478]:

Human MHC class II lymphocyte antigen (HLA-DP) beta chain mRNA

DNA sequence:

```
   1 agcgagtcct tcttttcctg actgcagctc ttttcatttt gccatccttc tccagctcca
  61 tgatggttct gcaggtttct gcggcccccc ggacagtggc tctgacggcg ttactgatgg
 121 tgctgctcac atctgtggtc cagggcaggg ccactccaga gaattacgtg taccagggac
 181 ggcaggaatg ctacgcgttt aatgggacac agcgcttcct ggagagatac atctacaacc
 241 gggaggagta cgcgcgcttc gacagcgacg tgggggagtt ccgggcggtg acggagctgg
 301 ggcggcctgc tgcggagtac tggaacagcc agaaggacat cctggaggag aagcgggcag
 361 tgccggacag ggtatgcaga cacaactacg agctggacga ggccgtgacc ctgcagcgcc
 421 gagtccagcc taaggtgaac gtttccccct ccaagaaggg gcccctgcag caccacaacc
 481 tgcttgtctg ccacgtgaca gatttctacc caggcagcat tcaagtccga tggttcctga
 541 atggacagga ggaaacagct ggggtcgtgt ccaccaacct gatccgtaat ggagactgga
 601 ccttccagat cctggtgatg ctggaaatga ccccccagca gggagacgtc tacatctgcc
 661 aagtggagca caccagcctg gacagtcctg tcaccgtgga gtggaaggca cagtctgatt
 721 ctgcccagag taagacattg acgggagctg ggggcttcgt gctggggctc atcatctgtg
 781 gagtgggcat cttcatgcac aggaggagca agaaagttca acgaggatct gcataaacag
 841 ggttcctgac ctcaccgaaa agactaatgt gccttagaac aagcatttgc tgtgttttgt
 901 taacacctgg ttccaggaca gaccctcagc ttcccaagag gatactgctg ccaagaagtt
 961 gctctgaagt cagtttctat cgttctgctc tttgattcaa agcactgttt ctctcactgg
1021 gcctccaacc atgttccctt cttcttagca ccacaaataa tcaaaaccca acataagtgt
1081 ttgctttcct ttaaaaatat gcatcaaatc gtctctcatt acttttctct gagggtttta
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1201 catcaaagtg gagatatgtt aactattgta taatgtggcc tgttatacat gacactcttc
1261 tgaattgact gtatttcagt gagctgcccc caaatcaagt ttagtgccct catccattta
1321 tgtctcagac cgctattctt aactattcaa tggtgagcag actgcaaatc tgcctgatag
1381 gacccatatt cccacagcac taattcaaca tatatcttac tgagagcatg ttttatcatt
1441 accattaaga agttaaatga acatcagaat ttaaaatcat aaatataatc taatacactt
1501 t
```

protein sequence:

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MMVLQVSAAPRTVALTALLMVLLTSVVQGRATPENYVYQGRQECYAFNGTQRFLERYIYNREEYARFDSDVGEFRAV
TELGRPAAEYWNSQKDILEEKRAVPDRVCRHNYELDEAVTLQRRVQPKVNVSPSKKGPLQHHNLLVCHVTDFYPGSI
QVRWFLNGQEETAGVVSTNLIRNGDWTFQILVMLEMTPQQGDVYICQVEHTSLDSPVTVEWKAQSDSAQSKTLTGA
GGFVLGLIICGVGIFMHRRSKKVQRGSA
```

Figure 12. (Page 14 of 33)

D83779. Human mRNA for KI...[gi:1228040]

Human mRNA for KIAA0195 gene, complete cds

1 cggacatggc tgcggccccc ggaggagggg acgtgaagtg aggaggggt tgggagggga
61 gaggacgcgg gcgaggaaga ccagccccgg ggccccgatg ttgtgactgt gacagactca
121 ctggggtttg tacatgctgg ggaggagcct tcctttcagg ggtgaccaca ttcatctggg
181 catgcctgca gtactcttgg cccatggacc tgaaggagaa gcacctgggc gagcctccct
241 cagccctggg cctgtccacg cggaaggccc tcagcgtcct gaaggagcag ctggaggcag
301 tgctggaagg acatctcagg gagcggaaga agtgtctgac gtggaaggag gtgtggagaa
361 gcagcttcct ccaccacagt aaccgctgct cctgcttcca ctggccgggg gcctcactca
421 tgctactggc cgtgctgctg ctgctgggct gctgcggggg acagccagcc gggagccgtg
481 gggtggggct ggtgaatgcc tcggccttgt tcctgttact gcttctcaac cttgtgctca
541 tcgggcggca agaccggctg aagcgtcggg aggtagagcg gaggctgcga gggatcattg
601 accaaatcca agatgccctc agggatggca gggagatcca gtggcccagt gccatgtatc
661 cagacctcca catgcctttt gcgccatcct ggtccttgca ctgggcctac agagacggac
721 acctggtcaa cctgccagtc agcctgctgg ttgaaggaga catcatagct ttgaggcctg
781 gccaggaatc gtttgcttct ctgaggggga tcaaggatga cgagcacatc gtcctggagc
841 cgggagacct cttccccccc ttctcccctc caccctcacc ccggggagaa gtggagagag
901 ggccacagag cccccagcag caccggcttt tccgtgtcct tgagacccct gtgattgaca
961 acatcagatg gtgcctggac atggccctgt cccgaccagt cactgccctg gacaatgagc
1021 ggttcacagt gcagtcggtg atgctacact atgctgtgcc cgtggtcctg gccggcttcc
1081 tcatcaccaa tgccctgcgc ttcatcttca gtgccccggg ggtcacttcc tggcagtaca
1141 ccctcctcca gctccaggtg aatggcgtcc tgcccatcct ccccctgctc tttccagtcc
1201 tctgggttct ggcaactgcc tgtggagagg cccgtgtcct ggcccagatg agcaaggcct
1261 cacccagctc cctgctggct aagttctcag aggatactct cagcagctat acggaggctg
1321 tctcctctca ggaaatgctg cgctgcattt ggggccactt cctgagggtg ctcgggggga
1381 catcgccaac gctgagccac agttccagcc tgctgcacag cctgggctct gtcacggtcc
1441 tgtgctgtgt ggacaaacag gggatcctgt catggccaaa tcccagccca gagactgtac
1501 tgttcttcag cgggaaggtg gagccccctc acagcagcca tgaggacctc accgatggcc
1561 tatccacccg ctccttctgc catcccgagc cccatgaacg agacgccctc ctggctggct
1621 ccctgaacaa caccctgcac ctttccaatg agcaggagcg tggcgactgg cctggcgagg
1681 ctcccaagcc ccccgagccc tattcacacc acaaagcgca tggccgcagc aaacacccat
1741 ctggctccaa cgtgagcttc agcagggaca ccgagggtgg tgaagaagag cccagcaaga
1801 cccagcctgg gatggagagc gacccctacg aagcagagga ctttgtgtgt gactaccacc
1861 tggagatgct gagcctgtcc caggaccagc agaacccctc ctgcatccag tttgatgact
1921 ccaactggca gctgcacctc acctccctca aacccctggg cctcaatgtg ctgctgaacc
1981 tgtgtgatgc cagcgtcacc gagcgcctgt gccgattctc cgaccacctg tgcaacattg
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2281 ccaccaccag cacagagcag atgctgtccc atggcaccgc tgatgtggtc ttagaggcct
2341 gcacagactt ctgggacgga gctgacatct accctctctc gggatctgac agaaagaaag
2401 tgctggactt ctaccagcga gcctgcctgt ctgggtattg ctctgccttc gcctacaagc
2461 ccatgaactg cgccctgtcc tctcagctca atggcaagtg catcgagctg gtacaggtgc
2521 ccggccaaag cagcatcttc accatgtgcg agctgcccag caccatcccc atcaagcaga
2581 acgcccgccg cagcagctgg agctctgacg aagggatcgg ggaggtgctg gagaaggaag
2641 actgcatgca ggccctgagc ggccagatct tcatgggcat ggtgtcctcc cagtaccagg
2701 cccggctgga catcgtgcgc ctcattgatg ggcttgtcaa cgcctgcatc cgctttgtct
2761 acttctcttt ggaggatgag ctcaaaagca aggtgtttgc agaaaaaatg ggcctggaga

Figure 12. (Page 15 of 33)

2821 caggctggaa ctgccacatc tccctcacac ccaatggtga catgcctggc tccgagatcc
2881 ccccctccag ccccagccac gcaggctccc tgcatgatga cctgaatcag gtgtcccgag
2941 atgatgcaga agggctcctc ctcatggagg aggagggcca ctcggacctc atcagcttcc
3001 agcctacgga cagcgacatc cccagcttcc tggaggactc caaccgggcc aagctgcccc
3061 ggggtatcca ccaagtgcgg ccccacctgc agaacattga caacgtgccc ctgctagtgc
3121 ccctttcac cgactgcacc ccagagacca tgtgtgagat gataaagatc atgcaagagt
3181 acggggaggt gacctgctgc ctgggcagct ctgccaacct gcggaacagc tgcctcttcc
3241 tccagagcga catcagcatt gccctggatc ccctgtaccc atcccgttgc tcctgggaga
3301 cctttggcta cgccaccagc atcagcatgg cccaggcctc ggatggcctt tctcccctgc
3361 agctgtcagg gcagctcaac agcctgccct gttccctgac ctttcgccag gaggagacca
3421 tcagcatcat ccggcttatc gaacaggctc ggcatgccac ctatggcatc cgtaagtgct
3481 tcctcttcct gctgcagtgc cagctgactc ttgtggtcat ccagttcctt tcttgcctgg
3541 tccagctgcc gccactcctg agtaccaccg acatcctgtg gctgtcctgc ttttgctacc
3601 ctctgctcag catctctctg ctggggaagc ccccccatag ctccatcatg tctatggcaa
3661 cggggaaaaa cctccagtcc attcccaaga agacccagca ctacttcctg ctctgcttcc
3721 tgctcaagtt cagcctcacc atcagctcct gcctcatctg ctttggcttc acactgcaga
3781 gcttctgtga cagctcccgg gaccgcaacc tcaccaactg ctcctccgtc atgctgccca
3841 gcaacgacga cagggctcca gcctggtttg aggactttgc caatggactg ctgtcggctc
3901 agaagctcac ggccgccctg attgtcctgc acactgtctt catttccatc acccatgtgc
3961 atcgcaccaa gcccctgtgg agaaagagcc ccttgaccaa cctctggtgg gccgtgacag
4021 tgcctgtggt gctgctgggt caggtggtcc agacggctgt ggacctgcag ctgtggacac
4081 acagggacag ccacgtccac tttggcctgg aggacgtgcc cctgctgaca tggctcctgg
4141 gctgcctgtc cctggtcctt gtggtggtga ccaatgagat cgtgaagcta catgagattc
4201 gggtccgagt ccgctaccag aagcgacaga agctgcagtt tgaaactaag ctgggcatga
4261 actctccctt ctgagccact ggctgtggtg gctgtagttg cccccgtccc tggggctaaa
4321 gccagaccca tttctgaaca ggggagtttg tatcatgaat gtttccaggt ttgctcctgc
4381 acccgtggca ctggaaaccc agctccccgt gtcagacccc gctgtcttcc tgagccctgg
4441 ggctcactgt ggaggagctg acggcctggg cccttggcca gtcctggctc ttccctgggc
4501 ctcaccaggg acactcttga atgtatggcc tcaggcgctc cctagagggg ccctaaaccc
4561 cctcacctgt gagctacccc ctttagggat cccttgcccc cttggagatc ccttgccccc
4621 cagtgcctct gctcgtgggt ccctggacac ggccttgaag ccaaccttct ttggaggagc
4681 aacagcagca gccttggccg acgcgtccaa ctcccaaggc tgccgtggag ggcaggggggg
4741 tggtgcttgc ctggatgtgg ccccgagtgc ctcccctccc tccctctgtg ggggagtctc
4801 ccgcctgaac ctgaagatgg agcagggccc ccgcttcgcc ctggagcctc ttcctgtgcc
4861 tggctcaagc tggctgcctg tcagtcttgg ggaatctggc ccaggtctcc tcagcctctg
4921 ccccagttct gggagaagtt tctactggtg tatatttttt actggaaatg agccttttag
4981 gaatgaatgt agactggttt gtattaaaat gtgtcaattg ct

Figure 12. (Page 16 of 33)

Protein sequence of Human KIAA0195

MDLKEKHLGEPPSALGLSTRKALSVLKEQLEAVLEGHLRERKKC
LTWKEVWRSSFLHHSNRCSCFHWPGASLMLLAVLLLLGCCGGQPAGSRGVGLVNASAL
FLLLLLNLVLIGRQDRLKRREVERRLRGIIDQIQDALRDGREIQWPSAMYPDLHMPFA
PSWSLHWAYRDGHLVNLPVSLLVEGDIIALRPGQESFASLRGIKDDEHIVLEPGDLFP
PFSPPPSPRGEVERGPQSPQQHRLFRVLETPVIDNIRWCLDMALSRPVTALDNERFTV
QSVMLHYAVPVVLAGFLITNALRFIFSAPGVTSWQYTLLQLQVNGVLPILPLLFPVLW
VLATACGEARVLAQMSKASPSSLLAKFSEDTLSSYTEAVSSQEMLRCIWGHFLRVLGG
TSPTLSHSSSLLHSLGSVTVLCCVDKQGILSWPNPSPETVLFFSGKVEPPHSSHEDLT
DGLSTRSFCHPEPHERDALLAGSLNNTLHLSNEQERGDWPGEAPKPPEPYSHHKAHGR
SKHPSGSNVSFSRDTEGGEEEPSKTQPGMESDPYEAEDFVCDYHLEMLSLSQDQQNPS
CIQFDDSNWQLHLTSLKPLGLNVLLNLCDASVTERLCRFSDHLCNIALQESHSAVLPV
HVPWGLCELARLIGFTPGAKELFKQENHLALYRLPSAETMKETSLGRLSCVTKRRPPL
SHMISLFIKDTTTSTEQMLSHGTADVVLEACTDFWDGADIYPLSGSDRKKVLDFYQRA
CLSGYCSAFAYKPMNCALSSQLNGKCIELVQVPGQSSIFTMCELPSTIPIKQNARRSS
WSSDEGIGEVLEKEDCMQALSGQIFMGMVSSQYQARLDIVRLIDGLVNACIRFVYFSL
EDELKSKVFAEKMGLETGWNCHISLTPNGDMPGSEIPPSSPSHAGSLHDDLNQVSRDD
AEGLLLMEEEGHSDLISFQPTDSDIPSFLEDSNRAKLPRGIHQVRPHLQNIDNVPLLV
PLFTDCTPETMCEMIKIMQEYGEVTCCLGSSANLRNSCLFLQSDISIALDPLYPSRCS
WETFGYATSISMAQASDGLSPLQLSGQLNSLPCSLTFRQEETISIIRLIEQARHATYG
IRKCFLFLLQCQLTLVVIQFLSCLVQLPPLLSTTDILWLSCFCYPLLSISLLGKPPHS
SIMSMATGKNLQSIPKKTQHYFLLCFLLKFSLTISSCLICFGFTLQSFCDSSRDRNLT
NCSSVMLPSNDDRAPAWFEDFANGLLSAQKLTAALIVLHTVFISITHVHRTKPLWRKS
PLTNLWWAVTVPVVLLGQVVQTAVDLQLWTHRDSHVHFGLEDVPLLTWLLGCLSLVLV
VVTNEIVKLHEIRVRVRYQKRQKLQFETKLGMNSPF

Figure 12. (Page 17 of 33)

L36719. Homo sapiens MAP ...[gi:685173]

Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds

```
   1 tggctggcaa tggccttgct gacctcgagc cgggcccacg tggggacctt tggagcacag
  61 cctacgatcc tggtgcaagg ccggtggatg cagaggccag tccatatacc acccaggcct
 121 gcgaggagcg tggtccccac ccatccagcc catatgtgca agtgcccttg acagagaggc
 181 tggtcatatc catggtgacc atttatgggc cacaacaggt ccccatctgc gcagtgaacc
 241 ctgtgctgag caccttgcag acgtgatctt gcttcgtcct gcagcactgt gcggggcagg
 301 aaaatccaag aggaagaagg atctacggat atcctgcatg tccaagccac ccgcacccaa
 361 ccccacaccc ccccggaacc tggactcccg gaccttcatc accattggag acagaaactt
 421 tgaggtggag gctgatgact tggtgaccat ctcagaactg ggccgtggag cctatggggt
 481 ggtagagaag gtgcggcacg cccagagcgg caccatcatg gccgtgaagc ggatccgggc
 541 caccgtgaac tcacaggagc agaagcggct gctcatggac ctggacatca acatgcgcac
 601 ggtcgactgt ttctacactg tcaccttcta cggggcacta ttcagagagg gagacgtgtg
 661 gatctgcatg gagctcatgg acacatcctt ggacaagttc taccggaagg tgctggataa
 721 aaacatgaca attccagagg acatccttgg ggagattgct gtgtctatcg tgcgggccct
 781 ggagcatctg cacagcaagc tgtcggtgat ccacagagat gtgaagccct ccaatgtcct
 841 tatcaacaag gagggccatg tgaagatgtg tgactttggc atcagtggct acttggtgga
 901 ctctgtggcc aagacgatgg atgccggctg caagccctac atggcccctg agaggatcaa
 961 cccagagctg aaccagaagg gctacaatgt caagtccgac gtctggagcc tgggcatcac
1021 catgattgag atggccatcc tgcggttccc ttacgagtcc tgggggaccc cgttccagca
1081 gctgaagcag gtggtggagg agccgtcccc ccagctccca gccgaccgtt tctccccga
1141 gtttgtggac ttcactgctc agtgcctgag gaagaacccc gcagagcgta tgagctacct
1201 ggagctgatg gagcacccct tcttcacctt gcacaaaacc aagaagacgg acattgctgc
1261 cttcgtgaag aagatcctgg gagaagactc ataggggctg ggcctcggac cccactccgg
1321 ccctccagag ccccacagcc ccatctgcgg gggcagtgct cacccacacc ataagctact
1381 gccatcctgg cccagggcat ctgggaggaa ccgagggggc tgctcccacc tggctctgtg
1441 gcgagccatt tgtcccaagt gccaaagaag cagaccattg gggctcccag ccaggccctt
1501 gtcggcccca ccagtgcctc tccctgctgc tcctaggacc cgtctccagc tgctgagatc
1561 ctggactgag ggggcctgga tgccccctgt ggatgctgct gcccctgcac agcaggctgc
1621 cagtgcctgg gtggatgggc caccgccttg cccagcctgg atgccatcca agttgtatat
1681 ttttttaatc tctcgactga atggactttg cacactttgg cccagggtgg ccacacctct
1741 atcccggctt tggtgcgggg tacacaagag gggatgagtt gtgtgaatac cccaagactc
1801 ccatgaggga gatgccatga gccgcccaag gccttcccct ggcactggca aacagggcct
1861 ctgcggagca cactggctca cccagtcctg cccgccaccg ttatcggtgt cattcacctt
1921 tcgtgttttt tttaatttat cctctgttga ttttttcttt tgctttatgg gtttggcttg
1981 tttttcttgc atggtttgga gctgatcgct tctcccccac cccctagggg
```

Protein sequence of Homo sapiens MAP kinase kinase 3 (MKK3)

```
MSKPPAPNPTPPRNLDSRTFITIGDRNFEVEADDLVTISELGRG
AYGVVEKVRHAQSGTIMAVKRIRATVNSQEQKRLLMDLDINMRTVDCFYTVTFYGALF
REGDVWICMELMDTSLDKFYRKVLDKNMTIPEDILGEIAVSIVRALEHLHSKLSVIHR
DVKPSNVLINKEGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINPELNQKGYNV
KSDVWSLGITMIEMAILRFPYESWGTPFQQLKQVVEEPSPQLPADRFSPEFVDFTAQC
LRKNPAERMSYLELMEHPFFTLHKTKKTDIAAFVKKILGEDS
```

Figure 12. (Page 18 of 33)

U47634. Human beta-tubuli...[gi:1297273]

Human beta-tubulin class III isotype (beta-3) mRNA, complete cds

```
   1 atgcgggaga tcgtgcacat ccaggccggc cagtgcggca accagatcgg ggccaagttc
  61 tgggaagtca tcagtgatga gcatggcatc gaccccagcg gcaactacgt gggcgactcg
 121 gacttgcagc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg
 181 cctcgagcca ttctggtgga cctggaaccc ggaaccatgg acagtgtccg ctcaggggcc
 241 tttggacatc tcttcaggcc tgacaatttc atctttggtc agagtggggc cggcaacaac
 301 tgggccaagg gtcactacac ggaggggggcg gagctggtgg attcggtcct ggatgtggtg
 361 cggaaggagt gtgaaaactg cgactgcctg cagggcttcc agctgaccca ctcgctgggg
 421 gggggacgg gctccggcat gggcacgttg ctcatcagca aggtgcgtga ggagtatccc
 481 gaccgcatca tgaacacctt cagcgtcgtg ccctcaccca aggtgtcaga cacggtggtg
 541 gaaccctaca acgccacgct gtccatccac cagctggtgg aaaacacgga tgaaacctac
 601 tgcatcgaca acgaggcgct ctacgacatc tgcttccgca ccctcaagct ggccacgccc
 661 acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cacctccttg
 721 cgcttcccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc
 781 ccgcgcctgc acttcttcat gcccggcttc gccccctca ccaggcgggg cagccagcag
 841 taccgggccc tgaccgtgcc cgagctcacc cagcagatgt tcgatgccaa gaacatgatg
 901 gccgcctgcg acccgcgcca cggccgctac ctgacggtgg ccaccgtgtt ccggggccgc
 961 atgtccatga aggaggtgga cgagcagatg ctggccatcc agagcaagaa cagcagctac
1021 ttcgtggagt ggatccccaa caacgtgaag gtggccgtgt gtgacatccc gccccgcggc
1081 ctcaagatgt cctccacctt catcgggaac agcacggcca tccaggagct gttcaagcgc
1141 atctccgagc agttcacggc catgttccgg cgcaaggcct tcctgcactg gtacacgggc
1201 gagggcatgg acgagatgga gttcaccgag gccgagagca acatgaacga cctggtgtcc
1261 gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgta cgaagacgac
1321 gaggaggagt cggaggccca gggccccaag tgaaactgct cgcagctgga gtgagaggca
1381 ggtggcggcc ggggccgaag ccagcagtgt ctaaaccccc ggagccatct tgctgccgac
1441 accctgcttt ccccatcgcc ctagggctcc cttgccgccc tcctgcagta tttatggcct
1501 cgtcctcccc cacctaggcc acgtgtgagc tgctcctgtc tctgtcttat tgcagctcca
1561 ggcctgacgt tttacggttt tgtttttttac tggtttgtgt ttatattttc ggggatactt
1621 aataaatcta ttgctgtcag ataccctt
```

Protein sequence of Human beta-tubulin class III isotype (beta-3)

```
MREIVHIQAGQCGNQIGAKFWEVISDEHGIDPSGNYVGDSDLQL
ERISVYYNEASSHKYVPRAILVDLEPGTMDSVRSGAFGHLFRPDNFIFGQSGAGNNWA
KGHYTEGAELVDSVLDVVRKECENCDCLQGFQLTHSLGGGTGSGMGTLLISKVREEYP
DRIMNTFSVVPSPKVSDTVVEPYNATLSIHQLVENTDETYCIDNEALYDICFRTLKLA
TPTYGDLNHLVSATMSGVTTSLRFPGQLNADLRKLAVNMVPFPRLHFFMPGFAPLTRR
GSQQYRALTVPELTQQMFDAKNMMAACDPRHGRYLTVATVFRGRMSMKEVDEQMLAIQ
SKNSSYFVEWIPNNVKVAVCDIPPRGLKMSSTFIGNSTAIQELFKRISEQFTAMFRRK
AFLHWYTGEGMDEMEFTEAESNMNDLVSEYQQYQDATAEEEGEMYEDDEEESEAQGPK
```

Figure 12. (Page 19 of 33)

M19267, Human tropomyosin...[gi:339943]

Human tropomyosin mRNA, complete cds

1 cagaatctcc ggcagttttt gtacctcaag aagtaagtgg aacacctttc cctgtcatag
61 ttattttcat ccagacatct ggtggaagca tcagattcct tacagatata agagaggcat
121 catttaaaag gtagaacagg atcgacaaac aaggatttat gtcaggatct ctcagcctct
181 gtgttaccga gggcatttct aacagtcttc ttactacggc ctccgccgac cgcgcgctcg
241 ccccgccgct cctgctgcag ccccagggcc cctcgccgcc gccaccatgg acgccatcaa
301 gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc
361 ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg agctggtgtc
421 actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa
481 agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt
541 agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg cccaggagcg
601 tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg agagtgagag
661 aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga
721 gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaaat atgaagaggt
781 ggcccgtaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc gggctgagct
841 ctcagaaggc caagtccgac agctggaaga acaattaaga ataatggatc agaccttgaa
901 agcattaatg gctgcagagg ataagtactc gcagaaggaa gacagatatg aggaagagat
961 caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg cggagaggtc
1021 agtaactaaa ttggagaaaa gcattgatga cttagaagag aaagtggctc atgccaaaga
1081 agaaaacctt agtatgcatc agatgctgga tcagacttta ctggagttaa acaacatgtg
1141 aaaacctcct tagctgcgac cacattcttt cattttgttt tgttttgttt tgtttttaaa
1201 cacctgctta ccccttaaat gcaatttatt tacttttacc actgtcacag aaacatccac
1261 aagataccag ctaggtcagg gggtggggaa aacacataca aaaagcaagc ccatgtcagg
1321 gcgatcctgg ttcaaatgtg ccatttcccg ggttgatgct gccacacttt gtagagagtt
1381 tagcaacaca gtgtgcttag tcagcgtagg aatcctcact aaagcaggag aagttccatt
1441 caaagtgcca atgatagagt caacaaggaa ggttaatgtt ggaaacacaa tcaggtgtgg
1501 attggtgcta ctttgaacaa aaggtccccc tgtggtcttt tgttcaacat tgtacaatgt
1561 agaactctgt ccaacactaa tttattttgt cttgagtttt actacaagat gagactatgg
1621 atcccgcatg cct

Protein sequence of Human tropomyosin

MDAIKKKMQMLKLDKENALDRAEQAEADKKAAEDRSKQLEDELV
SLQKKLKGTEDELDKYSEALKDAQEKLELAEKKATDAEADVASLNRRIQLVEEELDRA
QERLATALQKLEEAEKAADESERGMKVIESRAQKDEEKMEIQEIQLKEAKHIAEDADR
KYEEVARKLVIIESDLERAEERAELSEGQVRQLEEQLRIMDQTLKALMAAEDKYSQKE
DRYEEEIKVLSDKLKEAETRAEFAERSVTKLEKSIDDLEEKVAHAKEENLSMHQMLDQ
TLLELNNM

Figure 12. (Page 20 of 33)

S78798. 1-phosphatidylino...[gi:1042033]

1-phosphatidylinositol-4-phosphate 5-kinase isoform C [human, peripheral blood leukocytes, mRNA, 1835 nt]

```
   1 ttacacttta tacttccggc tcgaatattg tgtggaattg tgancggata acaatttcac
  61 acaggaaaca nctatgacct tgattacgcc aagctcgaaa ttaaccctca ctaaagggaa
 121 caaaagctgg agctcgcgcg cctgcaggtc gacactagtg gatccaaaga attcggcacg
 181 aggcgacggg cggagcggag cgcggcgcgc cggggccgcc gccgggggga tcggctgcct
 241 ccccgggccg ggtgtagaga gggcgggtcc ccggcctcgg gagcacggcg gtggagggga
 301 cataggaggc ggccatggcg acccccggca acctagggtc ctccgtcctg gcgagcaaga
 361 ccaagaccaa gaagaagcac ttcgtagcgc agaaagtgaa gctgtttcgg gccagcgacc
 421 cgctgctcag cgtcctcatg tgggggggtaa accactcgat caatgaactg agccatgttc
 481 aaatccctgt tatgttgatg ccagatgact tcaaagccta ttcaaaaata aaggtggaca
 541 atcacctttt taacaaagaa aacatgccga gccatttcaa gtttaaggaa tactgcccga
 601 tggtcttccg taactgcggg aagaggtttg gaattgatgt tcaagatttc cagaattccc
 661 tgaccaggag cgcacccctc cccaacgact cccaggcccg cagtggagct cgttttcaca
 721 cttcctacga caaaagatac atgatcaaga ctattaccag tgaagacgtg gccgaaatgc
 781 acaacatcct gaagaaatac caccagtaca tagtggaatg tcatgggatc acccttcttc
 841 cccacttgtt gggcatgtac cggcttaatg ttgatggagt tgaaatatat gtgatagtta
 901 caagaaatgt attcagccac cgtttgtctg tgtataggaa atacgactta aagggctcta
 961 cagtggctag agaagctagt gacaaagaaa aggccaaaga actgccaact ctgaaagata
1021 atgatttcat taatgagggc caaaagattt atattgatga caacagcaag aaggtcttcc
1081 tggaaaaact aaaaaaggat gttgagtttc tggcccagct gaagctcatg gactacagtc
1141 tgctggtggg aattcatgat gtggagagag ccgaacagga ggaagtggag tgtgaggaga
1201 acgatgggga ggaggagggc gagagcgatg gcacccaccc ggtgggaacc cccccagata
1261 gccccgggaa tacactgaac agctcaccac ccctggctcc cggggagttc gagccgaaca
1321 tcgacgtcta tggaattaag tgccatgaaa actcgcctag gaaggaggtg tacttcatgg
1381 caattattga catccttact cattatgatg caaaaaagaa agctgcccat gctgcaaaaa
1441 ctgttaaaca tggcgctggc gcggagatct ccaccgtgaa cccagaacag tattcaaagc
1501 gctttttgga ctttattggc cacatcttga cgtaacctcc tgcgcayctc ggacagcatg
1561 aacattggat ggacagaggt ggcttcggtg taggaaaaat gaaaaccaaa ctcagtgaag
1621 tactcatctt gcaggaagca aacctccttg tttacatctt caggccaaga tgactgattt
1681 gggggctact cgctttacag ctacctgatt ttcccagcat cgttctagct atttctgact
1741 ttgtgtatat gtgtgtgtgt gtgtgttggg gggggggtgag tgtgtgcccg cgtgtgcatt
1801 taaagcataa attaattaaa cagccacttc ggtca
```

Protein sequence of 1-phosphatidylinositol-4-phosphate 5-kinase isoform C

```
MATPGNLGSSVLASKTKTKKKHFVAQKVKLFRASDPLLSVLMWG
VNHSINELSHVQIPVMLMPDDFKAYSKIKVDNHLFNKENMPSHFKFKEYCPMVFRNCG
KRFGIDVQDFQNSLTRSAPLPNDSQARSGARFHTSYDKRYMIKTITSEDVAEMHNILK
KYHQYIVECHGITLLPHLLGMYRLNVDGVEIYVIVTRNVFSHRLSVYRKYDLKGSTVA
REASDKEKAKELPTLKDNDFINEGQKIYIDDNSKKVFLEKLKKDVEFLAQLKLMDYSL
LVGIHDVERAEQEEVECEENDGEEEGESDGTHPVGTPPDSPGNTLNSSPPLAPGEFEP
NIDVYGIKCHENSPRKEVYFMAIIDILTHYDAKKKAAHAAKTVKHGAGAEISTVNPEQ
YSKRFLDFIGHILT
```

Figure 12. (Page 21 of 33)

X58851. Human MLC1emb gen...[gi:34680]

Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1

1 aacagaatta gttggcccag ctctgcctat aagtagctga atgtcttgag gcaacttcaa
61 cgtttccctg gaccttagat tccttgcctg taaaacagca tggggccaga tgatctctaa
121 gggtccttct ggctctgaag gcaatgatct ggggcatgga acctgtagtt agagagctgg
181 gaaatgggca gatgtgggct ccagggcacc cagaattgca ggcttaggag ctaacagcaa
241 ccaggattct gtagtctagc aatcttgctt tacaggtgag gaaactgggc ctagaaaggc
301 gaagtgattt ttttgcctct ctcagcttta ttcctctttt cctctgaact gtagagtcta
361 aagattcagc acaaagcagt tttgtgtagt ggatacataa gctttttgt tgttattttt
421 ctgaattatt ttgttgactt tcaaagtttt ttttacataa acagtaaatg ctcgttataa
481 aaatttccat taatacagga agtgaaaaaa gtaaaaaact gcaaattgct gttatcctcc
541 cacccttacc ccctaggtcc ccagaggtgt ctctgttaac agttcagcgt gtatccatcc
601 tgactcctcc aataaatgca gaaacttgta tgtctctccc cgacaactgg attatcatat
661 acattattca agcataggct ttagactcag acatatctac atctaatccc agcttatagc
721 taattatttg agtgaccttg gccaagttgt tcatccagtt ttagtctcaa tctccccatg
781 tgtaaaatga aaataataat agtatctacc tggcctggcg tggcggctta tgcctataat
841 cccagccctt tggaagaccg aggctagtgg atcccttgag ctcaggagtt caagaccaac
901 ctgggcaatt tagcaagacc tcatctctac tgaaaaacaa aaaacaaaaa aactccccca
961 aaattagcca agtgtgctgg tgtgcacctg tagtcccagc tactcggaag gctgaggtgg
1021 gagaatcgct tgagccagga aagacgaggc tgcagtgagc tgtgattgca ccactgcact
1081 gcaacctgag caacagagcg ataccttgtt tctgttaaaa caaacaaaca aacaaaatag
1141 tatctacctt ataggatcat ggtgaagatt taatgagatt ttatatgaat agcacttaac
1201 agttcctggt actgatagta gtaagcacta cacacacaca cacacacaca cacacacaca
1261 cacacagagc acagaatgag ttagaggtaa agtgaaaact aaaccccaag ttttctgacc
1321 ctcagtctcc tcgactttct accacatctc tctgcttctc tcctaggtgc ctaggcatgg
1381 gttcagtgct cactacttgt tgaatgaatg actgaggttg tgtgtaaggg ggtagatcta
1441 gggatctgag gtctgtggag ttcctgggat gcctgctctg gaaaatggag gctttcatcc
1501 tgtgagttgg gagggtgtgg ggcagtgtgg gttggctgga ccagctgttg cttcagagct
1561 ccatgcctgg agagttgggc ctctaggcag agctgagggc ccagagtggc tctcagctta
1621 aaggatcttg gcttagaagg aatgtgcagt gggctgcctc tgctcgggag gggctaaaaa
1681 aagcctcacc ctcccctggg ctttgtgtga ggcttatcaa ctgctcaagt cagctcatct
1741 ctctggctgc tccggcatat ttgagaaggt ctgtttccct ggtccttctg ggtttccacc
1801 aattggcaag aagggatcag cctgtcctag aggtgaagag agagctgtgg catgaagggg
1861 agggggctgg tggccccaaa cctggtgaca atacacagtt gtcagctgta ccctgctggc
1921 gtttcttcct tttatagtca gcagcagttg ctcttgcttt cacccagccc ctctgtgggg
1981 ctcctgccca ggataaaagg gaagggaggc agcccaggct cctatctcat ctcccagacg
2041 ccacgtctct cggtttcttc ttagatcact cctctgccaa agatcccaac aagacaacat
2101 ggctcccaag aagcctgagc ctaagaagga ggcagccaag ccagctccag ctccagctcc
2161 agcccctgca ccagcccctg ccccagctcc tgaggctccc aaggaacctg cctttgaccc
2221 caagagtgta aaggtaagtg aggctcagcc attgggatag aggtggggat gacattgaga
2281 gtccttttgc tctggagctt agcgatctac tttatgtggg ctggactggg atgaggacta
2341 gggtgtccat gccccagatc gcagtcccat ggggcagtgg agtgggtgtt ggggctgatg
2401 agggggagat tgagtcataa acctttccg tcaagaatga ggtgctgctt tgagggagcc
2461 ctgtcctgct accctagatt tgtgcagcta agttgggaat ggggggaggt acaaccaacc
2521 atccatccac ccttttataa ggcattaatg aggaccacca tagcaaagta aa

Protein sequence of Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1

MAPKKPEPKKEAAKPAPAPAPAPAPAPAPEAPKEPAFDPKSV
KIDFTADQIEEFKEAFSLFDRTPTGEMKITYGQCGDVLRALGQNPTNAEVLRVLGKPK
PEEMNVKMLDFETFLPILQHISRNKEQGTYEDFVEGLRVFDKESNGTVMGAELRHVLA
TLGEKMTEAEVEQLLAGQEDANGCINYEAFVKHIMSG

Figure 12. (Page 22 of 33)

X90999. H.sapiens mRNA fo...[gi:1237212]

H.sapiens mRNA for Glyoxalase II

```
   1 gatttgcgga agaacctgac cgtggacgag ggcaccatga aggtagaggt gctgcctgcc
  61 ctgaccgaca actacatgta cctggtcatt gatgatgaga ccaaggaggc tgccattgtg
 121 gatccggtgc agccccagaa ggtcgtggac gcggcgagaa agcacggggt gaaactgacc
 181 acagtgctca ccacccacca ccactgggac catgctggcg ggaatgagaa actggtcaag
 241 ctggagtcgg gactgaaggt gtacgggggt gacgaccgta tcggggccct gactcacaag
 301 atcactcacc tgtccacact gcaggtgggg tctctgaacg tcaagtgcct ggcgaccccg
 361 tgccacactt caggacacat ttgttacttc gtgagcaagc ccggaggctc ggagcccccc
 421 gccgtgttca caggtgacac cttgtttgtg gctggctgcg ggaagttcta tgaagggact
 481 gcggatgaga tgtgtaaagc tctgctggag gtcttgggcc ggctcccccc ggacacaaga
 541 gtctactgtg gccacgagta caccatcaac aacctcaagt ttgcacgcca cgtggagccc
 601 ggcaatgccg ccatccggga gaagctggcc tgggccaagg agaagtacag catcggggag
 661 cccacagtgc catccaccct ggcagaggag tttacctaca acccccttcat gagagtgagg
 721 gagaagacgg tgcagcagca cgcaggtgag acggacccgg tgaccaccat gcgggccgtg
 781 cgcagggaga aggaccagtt caagatgccc cgggactgag gccgccctgc accttcagcg
 841 gatttgggga ttaggctctt ttaggtaact ggctttcctg ctggtccgtg cgggaaattc
 901 agtcttgatt taaccttaat tttacagccc ttggcttgtg ttatcggaca ttctaatgca
 961 tatttataag agaagtttaa caagtattta ttcccataaa aaaaaaaaaa a
```

Protein sequence of H.sapiens mRNA for Glyoxalase II

```
MKVEVLPALTDNYMYLVIDDETKEAAIVDPVQPQKVVDAARKHG
VKLTTVLTTHHHWDHAGGNEKLVKLESGLKVYGGDDRIGALTHKITHLSTLQVGSLNV
KCLATPCHTSGHICYFVSKPGGSEPPAVFTGDTLFVAGCGKFYEGTADEMCKALLEVL
GRLPPDTRVYCGHEYTINNLKFARHVEPGNAAIREKLAWAKEKYSIGEPTVPSTLAEE
FTYNPFMRVREKTVQQHAGETDPVTTMRAVRREKDQFKMPRD
```

Figure 12. (Page 23 of 33)

AF027515. Homo sapiens tran...[gi:2772909]
Homo sapiens trans-golgi network glycoprotein 48 (TGN) mRNA

```
   1 agaggggccc cgcgcgcgga tctcgcgaga gcattagagg gcggaagcgc tatccgagca
  61 ggatgcggtt cgtggttgcc ttggtcctcc tgaacgtcgc agcggcggga gccgtgccgc
 121 tcttggccac cgaaagcgtc aagcaagaag aagctggagt acggccttct gcaggaaacg
 181 tctccaccca ccccagcttg agccaacggc ctggaggctc taccaagtcg catccggagc
 241 cgcagactcc aaaagacagc cctagcaagt cgagtgcgga ggcgcagacc ccagaagaca
 301 cccccaacaa gtcgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtcgggtg
 361 cggaggcaca gacccccaaa ggcagcacta gcaagtcggg ttcggaggcg cagaccacaa
 421 aagacagcac tagtaagtcg catccggagc tgcagactcc aaaagacagc actggcaaat
 481 cgggtgcgga ggcgcagacc ccagaagaca gccccaacag gtcgggtgcg gagccaaaga
 541 cccaaaaaga cagccctagc aagtcaggtt cggaggcgca gaccacaaaa gatgtcccta
 601 ataagtcggg tgcggacggc cagaccccaa aagacggctc cagcaagtcg ggtgcggagg
 661 atcagacccc aaaagacgtc cctaacaagt cgggtgcgga gaagcagact ccaaaagacg
 721 gctctaacaa gtccggtgca gaggagcagg gcccaataga cgggcccagc aagtcgggtg
 781 cggaggagca gacctcaaaa gacagcccta acaaggtggt tccagagcag ccttcccgga
 841 aagaccattc caagcccatc tccaaccctt ctgataacaa ggagctcccc aaggctgaca
 901 caaaccagct tgctgacaaa gggaagcttt ctcctcatgc tttcaaaacc gaatctgggg
 961 aggaaactga cctcatttct ccccccgcagg aggaagttaa gtcttcagag cctactgagg
1021 atgtggggcc caaagaggct gaagatgatg atacaggacc cgaggagggc tcaccgccca
1081 aagaagagaa agaaaagatg tccggttctg cctccagtga gaaccgtgaa gggacacttt
1141 cggattccac gggtagcgag aaggatgacc tttatccgaa cggttctgga aatggcagcg
1201 cggagagcag ccacttcttt gcatatctgg tgactgcagc cattcttgtg gctgtcctct
1261 atatcgctca tcacaacaag cggaagatca ttgcttttgt cctggaagga aaaagatcta
1321 aagtcacccg gcggccaaag gccagtgact accaacgttt ggaccagaag atcttttctc
1381 ccccaagtcc taacagaatg gtatattcct ctggaaaaag atgaacgtca ccaatggatt
1441 gtgctgctct cgtttcagct ttgatttttt tgtccttgag aaccttgtcc tccctgctga
1501 tttgtttcta aatcaaaaga aatgaagaaa aaagtactgt gacctgagag acaccctcct
1561 ctagaattta gtggcgggtc tgggctggca gaggtagggg gctgctttgg gctttgcacc
1621 tgcactttgg tgacattgtt cttctgtgtt ccctttattt atgctggtgg cttccatccg
1681 ttctcctctg gggtgagtgg aggggtatat ggaaacacgg ctatgaccaa agggagatcc
1741 cagcctgggc agcctgcgct gctgaccacc ctccctgggg cccgggctct gtaggaaagt
1801 tggtccttga ctgtggcatt gcactctgca ctgtttctct ctgcagacct aggggaaaac
1861 tgcaggtgga agtgcttttc tactaaggcc tcttactttg ggggggatgt gccctacaga
1921 agacatagaa gatggggaaa tgccaatggg caaagagcta ctttgaatac ataattctct
1981 tcaaagactt cagcagcaaa cctaaacagc aggttaaaaa aaaagatgct tttttgggtg
2041 caagtctaac ctgtctagca tgagatcttc ttgattttct gattatttta tgtagcttga
2101 gacaaagtga atcaacttcc acttagttgt accgagcata aaacagaact tgggcttcct
2161 ggcagtgagg ccactgtccc atcacagatt tttaaaataa atatgatttg aagtagtgtg
2221 atctttcaca caa
```

Protein sequence of Homo sapiens trans-golgi network glycoprotein 48 (TGN)

```
MRFVVALVLLNVAAAGAVPLLATESVKQEEAGVRPSAGNVSTHP
SLSQRPGGSTKSHPEPQTPKDSPSKSSAEAQTPEDTPNKSGGEAKTLKDSSNKSGAEA
QTPKGSTSKSGSEAQTTKDSTSKSHPELQTPKDSTGKSGAEAQTPEDSPNRSGAEPKT
QKDSPSKSGSEAQTTKDVPNKSGADGQTPKDGSSKSGAEDQTPKDVPNKSGAEKQTPK
DGSNKSGAEEQGPIDGPSKSGAEEQTSKDSPNKVVPEQPSRKDHSKPISNPSDNKELP
KADTNQLADKGKLSPHAFKTESGEETDLISPPQEEVKSSEPTEDVGPKEAEDDDTGPE
EGSPPKEEKEKMSGSASSENREGTLSDSTGSEKDDLYPNGSGNGSAESSHFFAYLVTA
AILVAVLYIAHHNKRKIIAFVLEGKRSKVTRRPKASDYQRLDQKIFSPPSPNRMVYSS
GKR
```

Figure 12. (Page 24 of 33)

AJ223352. Homo sapiens mRNA...[gi:3255996]

Homo sapiens mRNA for for histone H2B

```
   1 gcggttcgcc ttcaacatgc cggaaccagc gaagtccgct cccgcgccca agaagggctc
  61 gaagaaagcc gtgactaagg cgcagaagaa ggacggtaag aagcgcaagc gcagccgcaa
 121 ggagagctac tccgtatacg tgtacaaggt gctgaagcag gtccaccccg acaccggcat
 181 ctcctctaag gccatgggaa tcatgaactc cttcgtcaac gacatcttcg aacgcatcgc
 241 gggtgaggct tcccgcctgg cgcattacaa caagcgctcg accatcacct ccagggagat
 301 ccagacggcc gtgcgcctgc tgctgcccgg ggagttggcc aagcacgccg tgtccgaggg
 361 caccaaggcc gtcaccaagt acaccagcgc taagtaaact tgccaaggag ggactttctc
 421 tggaatttcc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcggt
 481 tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt
 541 ccacaagcta aagctggcct cttgatctca ttcagattcc aaagagaatc atttacaagt
 601 taatttctgt ctccttggtc cattccttct ctttaataat catttactgt tcctcaaaga
 661 attgtttaca ttacccatct cctcttttgc tctgagaaag agtatataag cttctgtacc
 721 ccactggggg gttggggtaa tattctgtgg tcctcagccc tgtaccttaa taaatttgta
 781 tgccttttt tttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa
```

Protein sequence of human histone H2B

MPEPAKSAPAPKKGSKKAVTKAQKKDGKKRKRSRKESYSVYVYK
VLKQVHPDTGISSKAMGIMNSFVNDIFERIAGEASRLAHYNKRSTITSREIQTAVRLL
LPGELAKHAVSEGTKAVTKYTSAK

Figure 12. (Page 25 of 33)

L42542. Human RLIP76 prot...[gi:974142]

Human RLIP76 protein mRNA, complete cds

1 agtctggttt aactggttgg aacgactaaa gcacgctggc gcaaggaaag ctctcaactt
61 cgggagctga ggcgcaggct ggccagagcg tggagaggaa agccctttcc atcctcaagg
121 ccgttgcagg agatgcccgc gagccacctt cgccagcacc acaccggggt gtaatggata
181 ggtaacagag aagacctcgt cccttcctag tcagggcatc agcatgactg agtgcttcct
241 gccccccacc agcagcccca gtgaacaccg cagggtggag catggcagcg ggcttacccg
301 gacccccagc tctgaagaga tcagccctac taagtttcct ggattgtacc gcactggcga
361 gccctcacct ccccatgaca tcctccatga gcctcctgat gtagtgtctg atgatgagaa
421 agatcatggg aagaaaaaag ggaaatttaa gaaaaaggaa aagaggactg aaggctatgc
481 agcctttcag gaagatagct ctggagatga ggcagaaagt ccttctaaaa tgaagaggtc
541 caagggaatc catgttttca agaagcccag cttttctaaa aagaaggaaa aggattttaa
601 aataaaagag aaacccaaag aagaaaagca taaagaagaa aagcacaaag aagaaaaaca
661 taaagagaag aagtcaaaag acttgacagc agctgatgtt gttaaacagt ggaaggaaaa
721 gaagaaaaag aaaaagccaa ttcaggagcc agaggtgcct cagattgatg ttccaaatct
781 caaacccatt tttggaattc ctttggctga tgcagtagag aggaccatga tgtatgatgg
841 cattcggctg ccagccgttt tccgtgaatg tatagattac gtagagaagt atggcatgaa
901 gtgtgaaggc atctacagag tatcaggaat taaatcaaag gtggatgagc taaaagcagc
961 ctatgaccgg gaggagtcta caaacttgga agactatgag cctaacactg tagccagttt
1021 gctgaagcag tatttgcgag accttccaga gaatttgctt accaaagagc ttatgcccag
1081 atttgaagag gcttgtggga ggaccacgga gactgagaaa gtgcaggaat tccagcgttt
1141 actcaaagaa ctgccagaat gtaactatct tctgatttct tggctcattg tgcacatgga
1201 ccatgtcatt gcaaaggaac tggaaacaaa aatgaatata cagaacattt ctatagtgct
1261 cagcccaact gtgcagatca gcaatcgagt cctgtatgtg tttttcacac atgtgcaaga
1321 actctttgga aatgtggtac taaagcaagt gatgaaacct ctgcgatggt ctaacatggc
1381 cacgatgccc acgctgccag agacccaggc gggcatcaag gaggagatca ggagacagga
1441 gtttcttttg aattgtttac atcgagatct gcagggtggg ataaaggatt tgtctaaaga
1501 agaaagatta tgggaagtac aaagaatttt gacagccctc aaaagaaaac tgagagaagc
1561 taaaagacag gagtgtgaaa ccaagattgc acaagagata gccagtcttt caaaagagga
1621 tgtttccaaa gaagagatga atgaaaatga agaagttata aatattctcc ttgctcagga
1681 gaatgagatc ctgactgaac aggaggagct cctggccatg gagcagtttc tgcgccggca
1741 gattgcctca gaaaaagaag agattgaacg cctcagagct gagattgctg aaattcagag
1801 tcgccagcag cacggccgaa gtgagactga ggagtactcc tccgagagcg agagcgagag
1861 tgaggatgag gaggagctgc agatcattct ggaagactta cagagacaga acgaagagct
1921 ggaaataaag aacaatcatt tgaatcaagc aattcatgag gagcgcgagg ccatcatcga
1981 gctgcgcgtg cagctgcggc tgctccagat gcagcgagcc aaggccgagc agcaggcgca
2041 ggaggacgag gagcctgagt ggcgcggggg tgccgtccag ccgcccagag acggcgtcct
2101 tgagccaaaa gcagctaaag agcagccaaa ggcaggcaag gagccggcaa agccatcgcc
2161 cagcagggat aggaaggaga cgtccatctg agcagcctgc gtggccgtct ggagtccgtg
2221 agactgaaag gacccgtgca tcttactgta acccgggggc caggccggct ctctcgctgt
2281 acattctgta aaggtgtctt ctcttctcag actcttcctc tgtcacacgt ctgactcctt
2341 cacgtcaggc tcaggttcca tgggaggacg aagcagtgga cgcattgtgg gctttaggga
2401 cagatgagtt ttccagatag tgtcagctta tttgaagatt aattttcttt gttaacttaa
2461 aataactatt ttaacccttg agtggcttct ttttaaacca aaaaccgtct ttctttgctt
2521 ttttatcaca gcagaatcag gatctctttc tcattcaagg ggggaaccac accaggtcag
2581 cgctgcgcct gctgtggccg ccgcgagcca cgccctctgg gatctctggt accgtcactc
2641 ttgcttgtgc cttccacacc ttctcggtgc agatccctat gggggagctg cctcacgttc
2701 tctgactggt cagagcagcg cctggtgggt gttccctggc ccactctcct ctctccttct
2761 gcagttctaa accacagtct ataagcccga gtcaccagga cggcctgtct ggccacagac
2821 aggggctgcc tgtggagcct gcccaccggc ccccggcagt gcagtccagc ggggaggagg

Figure 12. (Page 26 of 33)

2881 ctgcccgttc ctgccagttc ctcactgcgg ggaccagcaa aggccttctc actgggttgg
2941 tcaaaggtag tcaccttggc ctggtgcatc cacagaggat gttgttcaaa ccagaaatct
3001 tttaaacgac tgaccttcct taaaaacaga atgactccga ttgcttgctt gggctagaat
3061 gtacacgtct ccttgcctga ataagccata tatatgctct taaacaaaag tttgaaatta
3121 tccatatcat ctcagtgaac ctactggtgg actcccaatt gacaagattg agcaatagaa
3181 aaaaattcct ttcctttgaa tgatagctgt gattcacccc accccatttt cttgtttctg
3241 gtccatccga tgagacggat gctctgatgc tctgaggctt ctgggaggct gggccctgga
3301 ggcaacgtgc tgcaggcgca ctctgtcaga gtgaacagca ccgcgagaca ggccaggctc
3361 gtggctcgga agacaaaccc cacacacact caaggggtcg aaaacaaacc ccacacgagg
3421 gctctcacct ccttctccta ggtagtattt attttcagca cctgtttgat gcagttttta
3481 atcctctacc tattgcactg ttgtgactcg ttggccatta tttgattttg gtacgaaaaa
3541 aagctttgtt atagaaatca gcatactatt tttttaaatc tggagagaag atattctggt
3601 gactgaaagt atggtcgggt gtcagatata aatgtgcaaa tgccttcttg ctgtcctgtc
3661 ggtctcagta cgttcacttt atagctgctg gcaatatcga aggttccttt tttgtttgtg
3721 taaactctaa tttctatcaa ggtgtcatgg atttttaaaa ttagtatttc attacaaatg
3781 tctcagcatt ggttaactaa ttttgggcag gaccattatt gatcaagcaa ataaattcaa
3841 cagccatttg ggaaaaag

Protein sequence of Human RLIP76

MTECFLPPTSSPSEHRRVEHGSGLTRTPSSEEISPTKFPGLYRT
GEPSPPHDILHEPPDVVSDDEKDHGKKKGKFKKKEKRTEGYAAFQEDSSGDEAESPSK
MKRSKGIHVFKKPSFSKKKEKDFKIKEKPKEEKHKEEKHKEEKHKEKKSKDLTAADVV
KQWKEKKKKKKPIQEPEVPQIDVPNLKPIFGIPLADAVERTMMYDGIRLPAVFRECID
YVEKYGMKCEGIYRVSGIKSKVDELKAAYDREESTNLEDYEPNTVASLLKQYLRDLPE
NLLTKELMPRFEEACGRTTETEKVQEFQRLLKELPECNYLLISWLIVHMDHVIAKELE
TKMNIQNISIVLSPTVQISNRVLYVFFTHVQELFGNVVLKQVMKPLRWSNMATMPTLP
ETQAGIKEEIRRQEFLLNCLHRDLQGGIKDLSKEERLWEVQRILTALKRKLREAKRQE
CETKIAQEIASLSKEDVSKEEMNENEEVINILLAQENEILTEQEELLAMEQFLRRQIA
SEKEEIERLRAEIAEIQSRQQHGRSETEEYSSESESESEDEEELQIILEDLQRQNEEL
EIKNNHLNQAIHEEREAIIELRVQLRLLQMQRAKAEQQAQEDEEPEWRGGAVQPPRDG
VLEPKAAKEQPKAGKEPAKPSPSRDRKETSI

Figure 12. (Page 27 of 33)

W26677. 11f7 Human retina...[gi:1305788]

TNNNNNTTNNNNNNTTNNCCTTGCTCAGCATTGGNTNTGATGTGCTGGTGGAGAACCACG
AAGAATGNATTGCTGAGGGGAGACCTGGTCCAGGGTCTTCTCCCCTGTAATCCAGGGCCA
CACTGATGAGNTCTGGGGGNTCTGCACACACCCCTCCCAGAACCGNTTCCTCACCTGCGG
CCACGACCGGNAGTTCTGCCTGTGGGATGGGGAGAGCCATGCACTGGCCTGGAGCATCGA
CCTCAAGGAGACTGGTCTCTGTGCTGACTTCCACCCGAGTGGGGCAGTTGTGGCCGNAGG
ACTGAACACGGGGAGGTGGTTGGTTTTGGNCACAGAGACCAGAGAGATCGTGTCTGATGT
CATTGATGGCAATNAGCAGCTCTCAGTGGTCCGGTACAGNCCAGATGGGTTGGTCCTGGC
CCAATTGGTTCCCCATNACAACNTNATNTTCAATCTTTTNGNGGTTTCCAGGGGATGGTG
CCCAATTCCAGNCCNTTTTGGGCCNTTTGTNTTTGGGTCAACNCCCAGNTTCAACCACTC
AATNTTGGAGTAGGTTCAANNNTTNGNNTTACCAGTTGNNNTTNTCCAANNNNNNNNNNN
NNTNTNNNNTNNTTNTTCTTTTNCNTNANNCNNNNNNNNNNCNNNTCTNCNTNTTNNTC
AANCCNNNTNNNNNNNCNNNCNNNNNCNTNTNNCTNCNTNNNNNCNNTNNNNCTNNTNNN
CNNNNNCTNNNNNTNNNCNNNNNNNN

Protein sequence of Human retina cDNA

No Protein sequence available from GenBank

Figure 12. (Page 28 of 33)

X51804. Human PMI gene fo...[gi:35534]

Human PMI gene for a putative receptor protein

1 ggcccccccc ccccctagaa atgctcgaac caggacggct cctggagtcc tcgcgccctc
61 gcagaaggac tacgggcccc ggcgaccccg ggggcggggc ttccggcgcg ctgccttgtg
121 ggcacggtag ttccgccggg tctggcttcc gcctgccgag cggccccgga ccgcaggccg
181 gactacactt cccgtcggcc cgcctgctct cccgatgccg ccttggcgcg agacgttggc
241 aagcagagtg tctccaagat ggccgcttgg ggaaggaggc gtcttggccc gggcagcagt
301 ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtgcatgag
361 atctacaatg gggagaatgc ccaagaccag tttgagtacg agctggagca ggccctggaa
421 gcccagtaca agtacattgt gattgagccc actcgcattg gcgacgagac agcccgctgg
481 atcaccgtgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctcttc
541 accccgttgg cgctgccctt agattattcc cactacattt ccctgcccgc tggtgtgctg
601 agcctggcct gctgcaccct ctatgggatc tcctggcagt ttgacccttg ctgcaagtac
661 caagtggagt acgacgccta taaactgtcg cgcctgcctc tgcacacact cacctcctcc
721 accccggtgg tgctggtccg gaaggacgac ctgcacagaa agagactgca caacacgata
781 gcactggccg ccctggtgta ctgtgtaaag aagatttacg aactctatgc cgtatgattt
841 cagtagaaca gggagcgaag caaaaccacc cggcccacaa gagacaacag agtattcaga
901 tcgccacact ctgtgaggca gcagagcctg ggcaggtgtt tggcttagta tttgttattt
961 ttaaaaaata acagatcacg ggtgtaccca gggtttttca gctcattaca ctaagatgtg
1021 gatttccata acccaagagg ggggtctgag gctgtggaag tccgactggg cagtggaatg
1081 ctgatggagg cagacgctgc cgaggggggtg tggacgtgct ttgggggagg tctttaagtc
1141 tattgtttaa ctgtaccatc cagagcccac cagaagctat tgatcattaa aattatgaga
1201 atttcaactc c

Protein sequence of Human PMI

MAAWGRRRLGPGSSGGSARERVSLSATDCYIVHEIYNGENAQDQ
FEYELEQALEAQYKYIVIEPTRIGDETARWITVGNCLHKTAVLAGTACLFTPLALPLD
YSHYISLPAGVLSLACCTLYGISWQFDPCCKYQVEYDAYKLSRLPLHTLTSSTPVVLV
RKDDLHRKRLHNTIALAALVYCVKKIYELYAV

Figure 12. (Page 29 of 33)

M24069. Human DNA-binding...[gi:181483]

Human DNA-binding protein A (dbpA) gene, 3' end

```
   1 gaattcgggc gggggagccc aaggagcgag cgcgccagac gaagctcgag ccgcctccgc
  61 cagcgcgacc ccacctcggc cgccggcctg cgccgcgaga tccgccccgg cctccccgag
 121 agcgagcccc ggccgccgcg accaccagcc gcgctaaccg ccgaccaacc gccaccgagg
 181 cgcctgagcg agagcagagg aggaggaggc atgagtgagg cgggcgaggc caccaccacc
 241 accaccacca ccctcccgca ggctccgacg gaggcggccg ccgcggctcc ccaggacccc
 301 gcgcccaaga gcccggtggg cagcggtgcg ccccaggccg cggccccggc gcccgccgcc
 361 cacgtcgcag gaaaccccgg tggggacgcg gcccctgcag ccacgggcac cgcggccgcc
 421 gcctctttag ccgccgccgc cggcagcgaa gacgcggaga aaaaagttct cgccaccaaa
 481 gtccttggca ctgtcaaatg gttcaacgtc agaaatggat atggatttat aaatcgaaat
 541 gacaccaaag aagatgtatt tgtacatcag actgccatca agaagaataa cccacggaaa
 601 tatctgcgca gtgtaggaga tggagaaact gtagagtttg atgtggttga aggagagaag
 661 ggtgcagaag ctgccaatgt gactggcccg gatggagttc ctgtggaagg gagtcgttac
 721 gctgcagatc ggcgccgtta cagacgtggc tactatggaa ggcgccgtgg ccctccccgg
 781 aattacgctg gggaggagga ggaggaaggg agcggcagca gtgaaggatt tgacccccct
 841 gccactgata ggcagttctc tggggcccgg aatcagctgc gccgccccca gtatcgccct
 901 cagtaccggc agcggcggtt cccgccttac cacgtgggac agacctttga ccgtcgctca
 961 cgggtcttac cccatcccaa cagaatacag gctggtgaga ttggagagat gaaggatgga
1021 gtcccagagg gagcacaact tcagggaccg gttcatcgaa atccaactta ccgcccaagg
1081 taccgtagca ggggacctcc tcgcccacga cctgccccag cagttggaga ggctgaagat
1141 aaagaaaatc agcaagccac cagtggtcca aaccagccgt ctgttcgccg tggataccgg
1201 cgtccctaca attaccggcg tcgcccgccg tcctcctaac gctccttcac aagatggcaa
1261 agaggccaag gcaggtgaag caccaactga gaaccctgct ccacccaccc agcagagcag
1321 tgtgagtaac accaggctcc tcaggcacct tcaccatcgg caggtggacc taaagaatta
1381 gatgaccatt cagaaataaa gcaaaaagca ggccacatac cttaaccaac accaaagaaa
1441 catccaagca ataaagtgga agactaacca agatttggac attggaatgt ttactgttat
1501 tctttaagaa acaactacaa aaagaaaatg tcaacaaatt tttccagcaa gctgagaacc
1561 tggaattc
```

Protein Sequence of Human DNA-binding protein A (dbpA)

EFGRGSPRSERARRSSSRLRQRDPTSAAGLRREIRPGLPESEPR
PPRPPAALTADQPPPRRLSESRGGGGMSEAGEATTTTTTTLPQAPTEAAAAAPQDPAP
KSPVGSGAPQAAAPAPAAHVAGNPGGDAAPAATGTAAAASLAAAAGSEDAEKKVLATK
VLGTVKWFNVRNGYGFINRNDTKEDVFVHQTAIKKNNPRKYLRSVGDGETVEFDVVEG
EKGAEAANVTGPDGVPVEGSRYAADRRRYRRGYYGRRRGPPRNYAGEEEEEGSGSSEG
FDPPATDRQFSGARNQLRRPQYRPQYRQRRFPPYHVGQTFDRRSRVLPHPNRIQAGEI
GEMKDGVPEGAQLQGPVHRNPTYRPRYRSRGPPRPRPAPAVGEAEDKENQQATSGPNQ
PSVRRGYRRPYNYRRRPPSS

Figure 12. (Page 30 of 33)

NM_002218. Homo sapiens inte...[gi:4504784]:

Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITIH4)

DNA sequence:

1 gtgagaagcc tcctggcaga cactggagcc acgatgaagc ccccaaggcc tgtccgtacc
61 tgcagcaaag ttctcgtcct gctttcactg ctggccatcc accagaccac tactgccgaa
121 aagaatggca tcgacatcta cagcctcacc gtggactcca gggtctcatc ccgatttgcc
181 cacacggtcg tcaccagccg agtggtcaat agggccaata cggtacagga ggccaccttc
241 cagatggagc tgcccaagaa agccttcatc accaacttct ccatgaacat cgatggcatg
301 acctacccag ggatcatcaa ggagaaggct gaagcccagg cacagtacag cgcagcagtg
361 gccaagggaa agaacgctgg cctcgtcaag gccaccggga gaaacatgga gcagttccag
421 gtgtcggtca gtgtggctcc caatgccaag atcacctttg agctggtcta tgaggagctg
481 ctcaagcggc gtttgggggt gtacgagctg ctgctgaaag tgcggcccca gcagctggtc
541 aagcacctgc agatggacat tcacatcttc gagccccagg gcatcagctt tctggagaca
601 gagagcacct tcatgaccaa ccagctggta gacgccctca ccacctggca gaataagacc
661 aaggctcaca tccggttcaa gccaacactt tcccagcagc aaaagtcccc agagcagcaa
721 gaaacagtcc tggacggcaa cctcattatc cgctatgatg tggaccgggc catctccggg
781 ggctccattc agatcgagaa cggctacttt gtacactact ttgcccccga gggcctaacc
841 acaatgccca agaatgtggt ctttgtcatt gacaagagcg gctccatgag tggcaggaaa
901 atccagcaga cccgggaagc cctaatcaag atcctggatg acctcagccc cagagaccag
961 ttcaacctca tcgtcttcag tacagaagca actcagtgga ggccatcact ggtgccagcc
1021 tcagccgaga acgtgaacaa ggccaggagc tttgctgcgg gcatccaggc cctgggaggg
1081 accaacatca atgatgcaat gctgatggct gtgcagttgc tggacagcag caaccaggag
1141 gagcggctgc ccgaagggag tgtctcactc atcatcctgc tcaccgatgg cgaccccact
1201 gtgggggaga ctaaccccag gagcatccag aataacgtgc gggaagctgt aagtggccgg
1261 tacagcctct tctgcctggg cttcggtttc gacgtcagct atgccttcct ggagaagctg
1321 gcactggaca atggcggcct ggcccggcgc atccatgagg actcagactc tgccctgcag
1381 ctccaggact tctaccagga agtggccaac ccactgctga cagcagtgac cttcgagtac
1441 ccaagcaatg ccgtggagga ggtcactcag aacaacttcc ggctcctctt caagggctca
1501 gagatggtgg tggctgggaa gctccaggac cgggggcctg atgtgctcac agccacagtc
1561 agtgggaagc tgcctacaca gaacatcact ttccaaacgg agtccagtgt ggcagagcag
1621 gaggcggagt tccagagccc caagtatatc ttccacaact tcatggagag gctctgggca
1681 tacctgacta tccagcagct gctggagcaa actgtctccg catccgacgc tgatcagcag
1741 gccctccgga accaagcgct gaatttatca cttgcctaca gctttgtcac gcctctcaca
1801 tctatggtag tcaccaaacc cgatgaccaa gagcagtctc aagttgctga gaagcccatg
1861 gaaggcgaaa gtagaaacag gaatgtccac tcaggttcca ctttcttcaa atattatctc
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1981 caagctggag ctgctggctc ccggatgaat ttcagacctg gggttctcag ctccaggcaa
2041 cttggactcc caggacctcc tgatgttcct gaccatgctg cttaccaccc cttccgccgt
2101 ctggccatct tgcctgcttc agcaccacca gccacctcaa atcctgatcc agctgtgtct
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2281 cccagacacc gccaggggcc agtgaacctg ctctcagacc ctgagcaagg ggttgaggtg
2341 actggccagt atgagaggga gaaggctggg ttctcatgga tcgaagtgac cttcaagaac
2401 cccctggtat gggttcacgc atcccctgaa cacgtggtgg tgactcggaa ccgaagaagc
2461 tctgcgtaca agtggaagga gacgctattc tcagtgatgc ccggcctgaa gatgaccatg
2521 gacaagacgg gtctcctgct gctcagtgac ccagacaaag tgaccatcgg cctgttgttc
2581 tgggatggcc gtggggaggg gctccggctc cttctgcgtg acactgaccg cttctccagc
2641 cacgttggag ggacccttgg ccagttttac caggaggtgc tctggggatc tccagcagca
2701 tcagatgacg gcagacgcac gctgagggtt cagggcaatg accactctgc caccagagag

Figure 12. (Page 31 of 33)

2761 cgcaggctgg attaccagga ggggcccccg ggagtggaga tttcctgctg gtctgtggag
2821 ctgtagttct gatggaagga gctgtgccca ccctgtacac ttggcttccc cctgcaactg
2881 cagggccgct tctggggcct ggaccaccat ggggaggaag agtcccactc attacaaata
2941 aagaaaggtg gtgtgagcct ggg

Protein sequence for Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITIH4):

MKPPRPVRTCSKVLVLLSLLAIHQTTTAEKNGIDIYSLTVDSRVSSRFAHTVVTSRVVNRANTVQEATFQMELPKKAFIT
NFSMNIDGMTYPGIIKEKAEAQAQYSAAVAKGKNAGLVKATGRNMEQFQVSVSVAPNAKITFELVYEELLKRRLGVYE
LLLKVRPQQLVKHLQMDIHIFEPQGISFLETESTFMTNQLVDALTTWQNKTKAHIRFKPTLSQQQKSPEQQETVLDGNL
IIRYDVDRAISGGSIQIENGYFVHYFAPEGLTTMPKNVVFVIDKSGSMSGRKIQQTREALIKILDDLSPRDQFNLIVFSTE
ATQWRPSLVPASAENVNKARSFAAGIQALGGTNINDAMLMAVQLLDSSNQEERLPEGSVSLIILLTDGDPTVGETNPR
SIQNNVREAVSGRYSLFCLGFGFDVSYAFLEKLALDNGGLARRIHEDSDSALQLQDFYQEVANPLLTAVTFEYPSNAV
EEVTQNNFRLLFKGSEMVVAGKLQDRGPDVLTATVSGKLPTQNITFQTESSVAEQEAEFQSPKYIFHNFMERLWAYL
TIQQLLEQTVSASDADQQALRNQALNLSLAYSFVTPLTSMVVTKPDDQEQSQVAEKPMEGESRNRNVHSGSTFFKYY
LQGAKIPKPEASFSPRRGWNRQAGAAGSRMNFRPGVLSSRQLGLPGPPDVPDHAAYHPFRRLAILPASAPPATSNP
DPAVSRVMNMKIEETTMTTQTPAPIQAPSAILPLPGQSVERLCVDPRHRQGPVNLLSDPEQGVEVTGQYEREKAGFS
WIEVTFKNPLVWVHASPEHVVVTRNRRSSAYKWKETLFSVMPGLKMTMDKTGLLLLSDPDKVTIGLLFWDGRGEGLR
LLLRDTDRFSSHVGGTLGQFYQEVLWGSPAASDDGRRTLRVQGNDHSATRERRLDYQEGPPGVEISCWSVEL

Figure 12. (Page 32 of 33)

NM_000584. Homo sapiens interleukin 8 (IL8), mRNA.[gi:28610153]

1 ctccataagg cacaaacttt cagagacagc agagcacaca agcttctagg acaagagcca
61 ggaagaaacc accggaagga accatctcac tgtgtgtaaa catgacttcc aagctggccg
121 tggctctctt ggcagccttc ctgatttctg cagctctgtg tgaaggtgca gttttgccaa
181 ggagtgctaa agaacttaga tgtcagtgca taaagacata ctccaaacct ttccacccca
241 aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaac acagaaatta
301 ttgtaaagct ttctgatgga agagagctct gtctggaccc caaggaaaac tgggtgcaga
361 gggttgtgga gaagtttttg aagagggctg agaattcata aaaaaattca ttctctgtgg
421 tatccaagaa tcagtgaaga tgccagtgaa acttcaagca aatctacttc aacacttcat
481 gtattgtgtg ggtctgttgt agggttgcca gatgcaatac aagattcctg gttaaatttg
541 aatttcagta aacaatgaat agtttttcat tgtaccatga aatatccaga acatacttat
601 atgtaaagta ttatttattt gaatctacaa aaaacaacaa ataatttta aatataagga
661 ttttcctaga tattgcacgg gagaatatac aaatagcaaa attgaggcca agggccaaga
721 gaatatccga actttaattt caggaattga atgggtttgc tagaatgtga tatttgaagc
781 atcacataaa aatgatggga caataaattt tgccataaag tcaaatttag ctggaaatcc
841 tggatttttt tctgttaaat ctggcaaccc tagtctgcta gccaggatcc acaagtcctt
901 gttccactgt gccttggttt ctcctttatt tctaagtgga aaaagtatta gccaccatct
961 tacctcacag tgatgttgtg aggacatgtg gaagcacttt aagttttttc atcataacat
1021 aaattatttt caagtgtaac ttattaacct atttattatt tatgtattta tttaagcatc
1081 aaatatttgt gcaagaattt ggaaaaatag aagatgaatc attgattgaa tagttataaa
1141 gatgttatag taaatttatt ttattttaga tattaaatga tgttttatta gataaatttc
1201 aatcagggtt tttagattaa acaaacaaac aattgggtac ccagttaaat tttcatttca
1261 gataaacaac aaataatttt ttagtataag tacattattg tttatctgaa attttaattg
1321 aactaacaat cctagtttga tactcccagt cttgtcattg ccagctgtgt tggtagtgct
1381 gtgttgaatt acggaataat gagttagaac tattaaaaca gccaaaactc cacagtcaat
1441 attagtaatt tcttgctggt tgaaacttgt ttattatgta caaatagatt cttataatat
1501 tatttaaatg actgcatttt taaatacaag gctttatatt tttaacttta agatgttttt
1561 atgtgctctc caaatttttt ttactgtttc tgattgtatg gaaatataaa agtaaatatg
1621 aaacatttaa aatataattt gttgtcaaag taaaaaaaaa aaaaaa

Protein sequence for Interleukin 8 precursor

1 mtsklavall aaflisaalc egavlprsak elrcqcikty skpfhpkfik elrviesgph
61 canteiivkl sdgrelcldp kenwvqrvve kflkraens

Figure 12. (Page 33 of 33)

M11725. Human C-reactive protein gene, complete cds.[gi:181067]

```
   1 tttgcttccc ctcttcccga agctctgaca cctgccccaa caagcaatgt tggaaaatta
  61 tttacatagt ggcgcaaact cccttactgc tttggatata aatccaggca ggaggaggta
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 181 ccaaaggagt gaattcaggc ccttgtatca ctggcagcag gacgtgacca tggagaagct
 241 gttgtgtttc ttggtcttga ccagcctctc tcatgctttt ggccagacag gtaagggcca
 301 ccccaggcta tgggagagtt ttgatctgag gtatgggggt ggggtctaag actgcatgaa
 361 cagtctcaaa aaaaaaaaaa aaagactgta tgaacagaac agtggagcat ccttcatggt
 421 gtgtgtgtgt gtgtgtgtgt gtgtgtgtgg tgtgtaactg gagaaggggt cagtctgttt
 481 ctcaatctta aattctatac gtaagtgagg ggatagatct gtgtgatctg agaaacctct
 541 cacatttgct tgtttttctg gctcacagac atgtcgagga aggcttttgt gtttcccaaa
 601 gagtcggata cttcctatgt atccctcaaa gcaccgttaa cgaagcctct caaagccttc
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1081 atctatcttg gcgggccctt cagtcctaat gtcctgaact ggcgggcact gaagtatgaa
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1261 gctttttac actgcatggt tcccacgtct ctgtctctgg gcctttgttc ccctatatgc
1321 attgaggcct gctccaccct cctcagcgcc tgagaatgga ggtaaagtgt ctggtctggg
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1441 catttttatt tcaagttgga cagatcttgg agataatttc ttacctcaca tagatgagaa
1501 aactaacacc cagaaaggag aaatgatgtt ataaaaaact cataaggcaa gagctgagaa
1561 ggaagcgctg atcttctatt taattcccca cccatgaccc ccagaaagca ggagcattgc
1621 ccacattcac agggctcttc agtctcagaa tcaggacact ggccaggtgt ctggtttggg
1681 tccagagtgc tcatcatcat gtcatagaac tgctgggccc aggtctcctg aaatgggaag
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2041 ggtgtcctgt cagaggagcc catctcccat ctccccagct ccctatctgg aggatagttg
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2161 ttgggagtga gacatcttct tgctgctgga tttccaagct gagaggacgt gaacctggga
2221 ccaccagtag ccatcttgtt tgccacatgg agagagactg tgaggacaga agccaaactg
2281 gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa
2341 tcagccttgt ctggaaccag atctacacct ggactgccca ggtctataag ccaataaagc
2401 ccctgtttac ttgagtgagt ccaagctgtt ttctgatagt tgctttagaa gttgtgacta
2461 acttctctat gacctttgaa
```

Protein sequence for C-reactive protein

```
   1 meklicflvl tslshafgqt dmsrkafvfp kesdtsyvsl kapltkplka ftvclhfyte
  61 lsstrgysif syatkrqdne ilifwskdig ysftvggsei lfevpevtva pvhictswes
 121 asgivefwvd gkprvrksik kgytvgaeas iilgqeqdsf ggnfegsqsl vgdignvnmw
 181 dfvlspdein tiylggpfsp nvlnwralky evqgevftkp qlwp
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Figure 13.

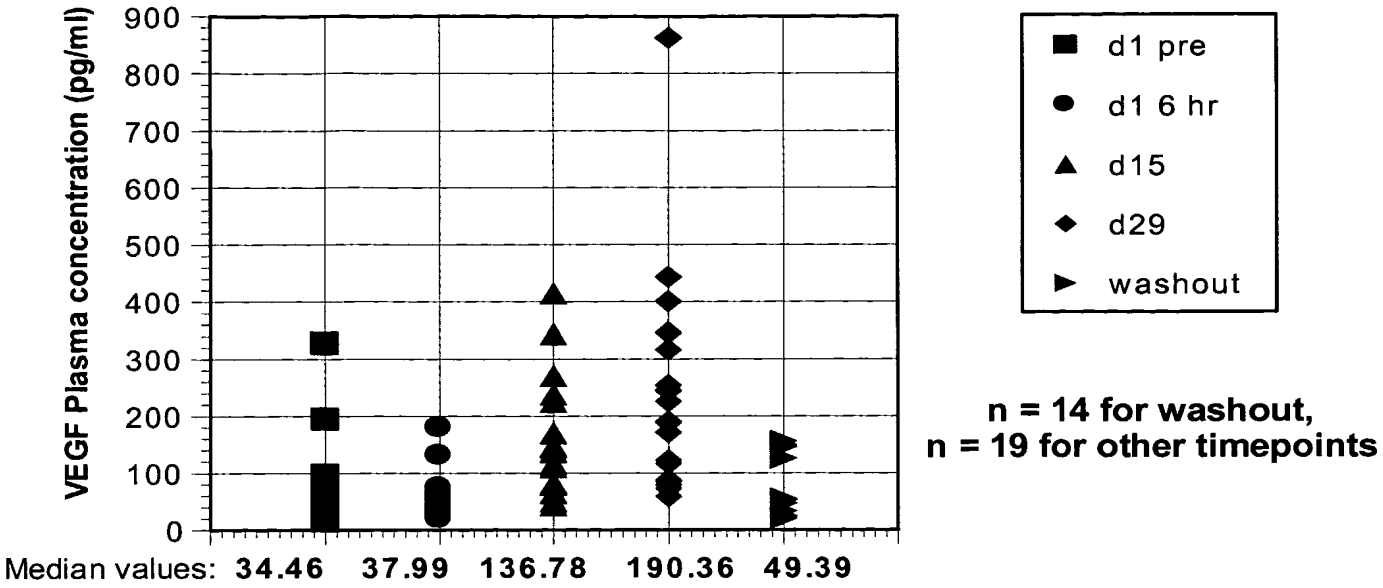
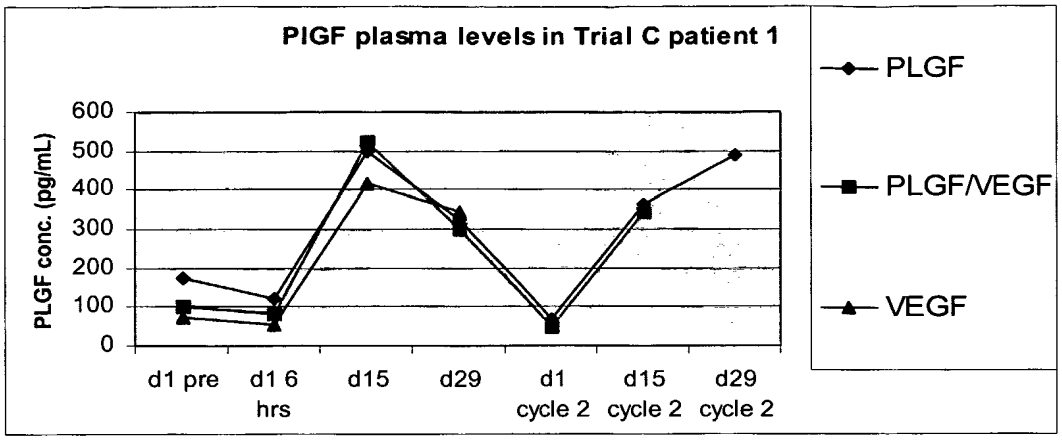
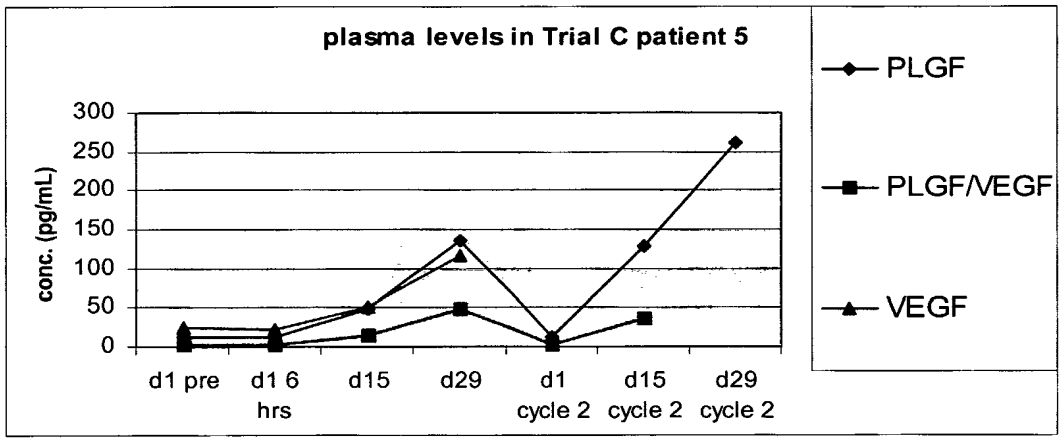

VEGF Plasma concentration (pg/ml)
900
800
700
600
500
400
300
200
100
0
Median values: 34.46 37.99 136.78 190.36 49.39
d1 pre
d1 6 hr
d15
d29
washout
n = 14 for washout,
n = 19 for other timepoints

Figure 14.


PIGF plasma levels in Trial C patient 1
PLGF conc. (pg/mL)
600
500
400
300
200
100
0
d1 pre
d1 6 hrs
d15
d29
d1 cycle 2
d15 cycle 2
d29 cycle 2
PLGF
PLGF/VEGF
VEGF


plasma levels in Trial C patient 5
conc. (pg/mL)
300
250
200
150
100
50
0
d1 pre
d1 6 hrs
d15
d29
d1 cycle 2
d15 cycle 2
d29 cycle 2
PLGF
PLGF/VEGF
VEGF

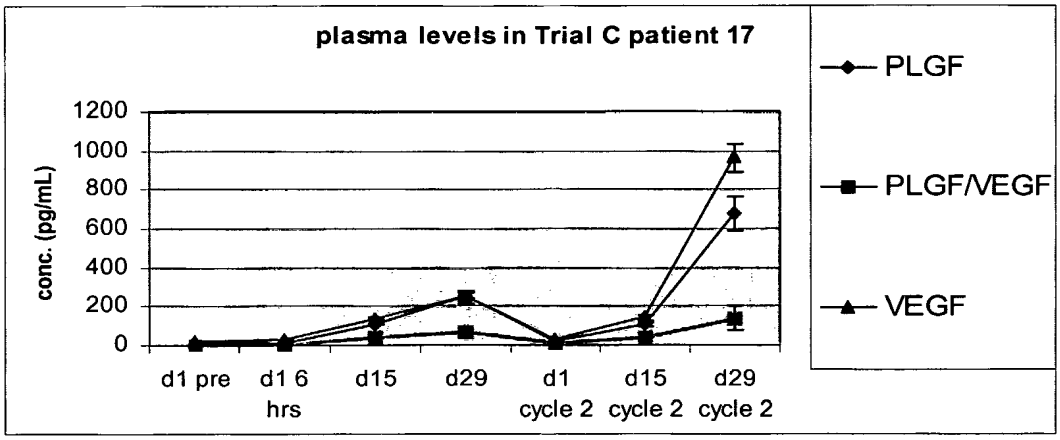
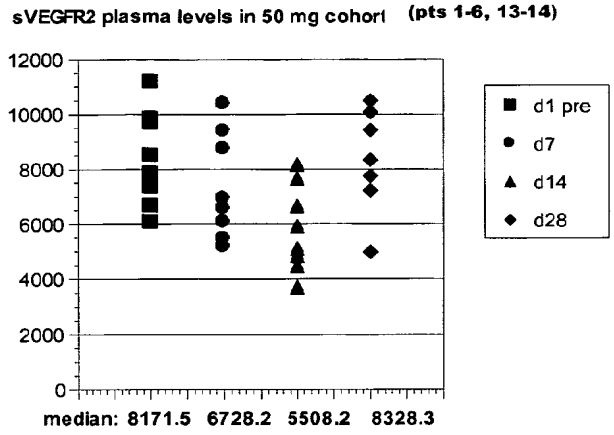
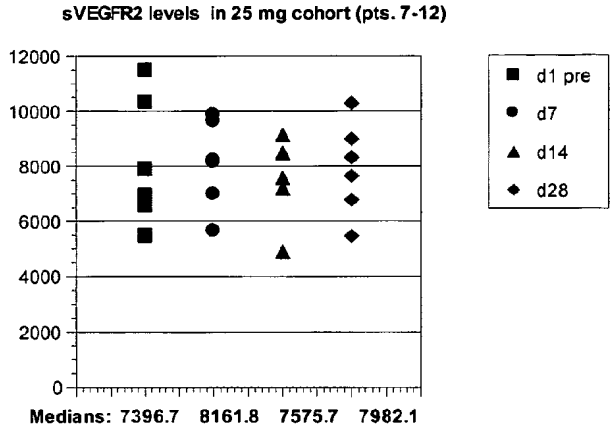

plasma levels in Trial C patient 17
conc. (pg/mL)
1200
1000
800
600
400
200
0
d1 pre
d1 6 hrs
d15
d29
d1 cycle 2
d15 cycle 2
d29 cycle 2
PLGF
PLGF/VEGF
VEGF

Figure 15.





Graphs above display plasma levels of sVEGFR2 in individual patients, either 50 mg daily (A) or 25 mg daily (B). The table at right displays results of t-test analysis comparing sVEGFR2 plasma concentrations at end of dosing (d14) to day 1 or at end of cycle 1 washout (d28) to day 1.

	d14 v d1	d28 v d1
50 mg cohort	0.0076	0.94
25 mg cohort	0.611	0.87

t-test comparisons of sVEGFR2 levels in two cohorts

Figure 16.

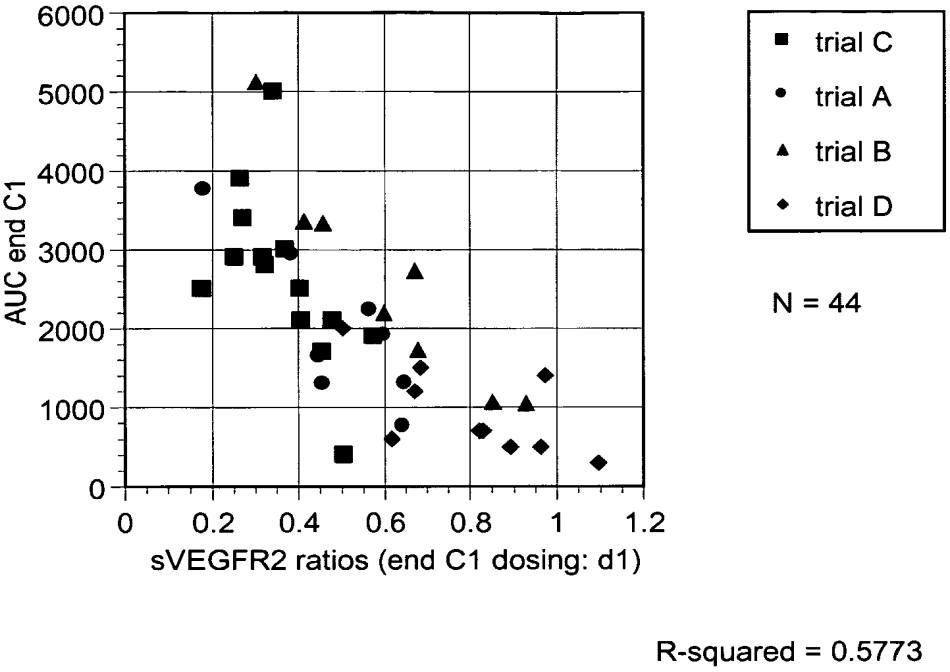
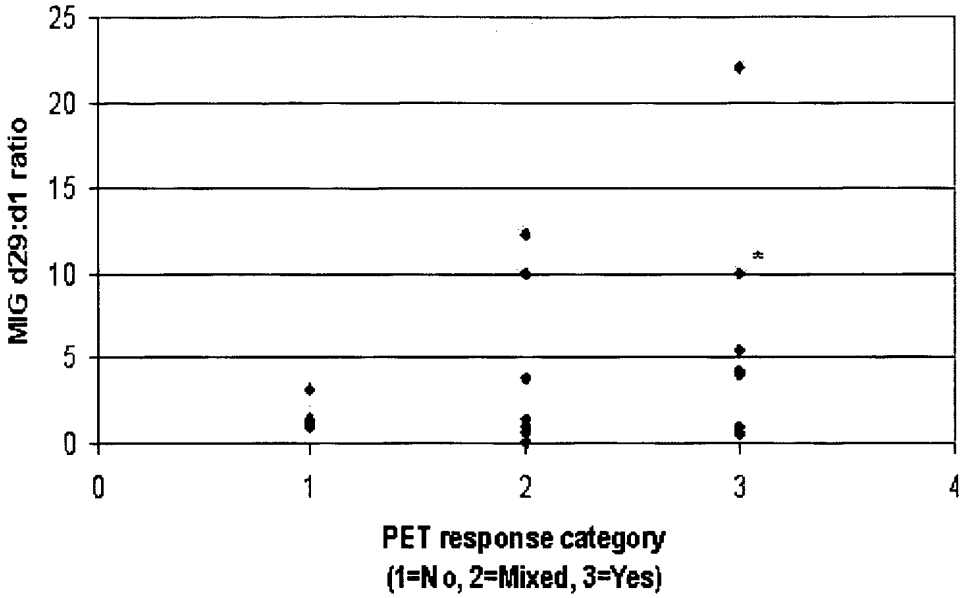

6000
5000
4000
3000
2000
1000
0
AUC end C1
0
0.2
0.4
0.6
0.8
1
1.2
sVEGFR2 ratios (end C1 dosing: d1)
trial C
trial A
trial B
trial D
N = 44
R-squared = 0.5773

Figure 17.



1: n = 6. 2: n = 8. 3: n = 8

*estimated minimum ratio

Figure 18.

NP_003367 vascular endothelial growth factor [gi:19923240]

1 mnfllswvhw slalllylhh akwsqaapma egggqnhhev vkfmdvyqrs ychpietlvd
61 ifqeypdeie yifkpscvpl mrcggcsnde glecvptees nitmqimrik phqgqhigem
121 sflqhnkcec rpkkdrarqe npcgpcserr khlfvqdpqt ckcsckncths rckarqleln
181 ertcrcdkpr r

Figure 19.

P49763 Placenta growth factor [gi:17380553]

1 mpvmrlfpcf lqllaglalp avppqqwals agngssevev vpfqevwgrs ycralerlvd
61 vvseypseve hmfspscvsl lrctgccgde nlhcvpveta nvtmqllkir sgdrpsyvel
121 tfsqhvrcec rhspgrqspd mpgdfradap sflpprrslp mlfrmewgca ltgsqsavwp
181 sspvpeeipr mhpgrngkkq qrkplrekmk percgdavpr r

Figure 20.

P35968 Vascular endothelial growth factor receptor 2 [gi:9087218]

1 mqskvllava lwlcvetraa svglpsvsld lprlsiqkdi ltikanttlq itcrgqrdld
61 wlwpnnqsgs eqrvevtecs dglfcktlti pkvigndtga ykcfyretdl asviyvyvqd
121 yrspfiasvs dqhgvvyite nknktvvipc lgsisnlnvs lcarypekrf vpdgnriswd
181 skkgftipsy misyagmvfc eakindesyq simyivvvvg yriydvvlsp shgielsvge
241 klvlnctart elnvgidfnw eypsskhqhk klvnrdlktq sgsemkkfls tltidgvtrs
301 dqglytcaas sglmtkknst fvrvhekpfv afgsgmeslv eatvgervri pakylgyppp
361 eikwykngip lesnhtikag hvltimevse rdtgnytvil tnpiskekqs hvvslvvyvp
421 pqigekslis pvdsyqygtt qtltctvyai ppphhihwyw qleeecanep sqavsvtnpy
481 pceewrsved fqggnkievn knqfaliegk nktvstlviq aanvsalykc eavnkvgrge
541 rvisfhvtrg peitlqpdmq pteqesvslw ctadrstfen ltwyklgpqp lpihvgelpt
601 pvcknldtlw klnatmfsns tndilimelk naslqdqgdy vclaqdrktk krhcvvrqlt
661 vlervaptit gnlenqttsi gesievscta sgnpppqimw fkdnetlved sgivlkdgnr
721 nltirrvrke deglytcqac svlgcakvea ffiiegaqek tnleiiilvg taviamffwl
781 llviilrtvk ranggelktg ylsivmdpde lpldehcerl pydaskwefp rdrlklgkpl
841 grgafgqvie adafgidkta tcrtvavkml kegathsehr almselkili highhlnvvn
901 llgactkpgg plmvivefck fgnlstylrs krnefvpykt kgarfrqgkd yvgaipvdlk
961 rrldsitssq ssassgfvee kslsdveeee apedlykdfl tlehlicysf qvakgmefla
1021 srkcihrdla arnillsekn vvkicdfgla rdiykdpdyv rkgdarlplk wmapetifdr
1081 vytiqsdvws fgvllweifs lgaspypgvk ideefcrrlk egtrmrapdy ttpemyqtml
1141 dcwhgepsqr ptfselvehl gnllqanaqq dgkdyivlpi setlsmeeds glslptspvs
1201 cmeeeevcdp kfhydntagi sqylqnskrk srpvsvktfe dipleepevk vipddnqtds
1261 gmvlaseelk tledrtklsp sfggmvpsks resvasegsn qtsgyqsgyh sddtdttvys
1321 seeaellkli eigvqtgsta qilqpdsgtt lssppv

Figure 21.

Q07325 Small inducible cytokine B9 precursor (CXCL9) (Gamma interferon induced monokine) (MIG) [gi:585487]

1 mkksgvlfll giillvligv qgtpvvrkgr cscistnqgt ihlqslkdlk qfapspscek
61 ieiiatlkng vqtclnpdsa dvkelikkwe kqvsqkkkqk ngkkhqkkkv lkvrksqrsr
121 qkktt

Figure 22.

NP_001556 interferon-inducible cytokine IP-10 [gi:4504701]

1 mnqtailicc lifltlsgiq gvplsrtvrc tcisisnqpv nprsleklei ipasqfcprv
61 eiiatmkkkg ekrclnpesk aiknllkavs kemskrsp

Figure 23.

O14625 Interferon-inducible T-cell alpha chemoattractant (I-TAC)[gi:7674360]

1 msvkgmaial avilcatvvq gfpmfkrgrc lcigpgvkav kvadiekasi mypsnncdki
61 eviitlkenk gqrclnpksk qarliikkve rknf

Figure 24. (Page 1 of 46)

M33308. Human vinculin mR...[gi:340236]

Human vinculin mRNA, complete cds

1 gaattccact tctctgtcgc ccgcggttcg ccgccccgct cgccgccgcg atgccagtgt
61 ttcatacgcg cacgatcgag agcatcctgg agccggtggc acagcagatc tcccacctgg
121 tgataatgca cgaggagggc gaggtggacg gcaaagccat tcctgacctc accgcgcccg
181 tggccgccgt gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa
241 ccactgagga tcagattttg aagagagata tgccaccagc atttattaag gttgagaatg
301 cttgcaccaa gcttgtccag gcagctcaga tgcttcagtc agacccttac tcagtgcctg
361 ctcgagatta tctaattgat gggtcaaggg gcatcctctc tggaacatca gacctgctcc
421 ttaccttcga tgaggctgag gtccgtaaaa ttattagagt ttgcaaagga attttggaat
481 atcttacagt ggcagaggtg gtggagacta tggaagattt ggtcacttac acaaagaatc
541 ttgggccagg aatgactaag atggccaaga tgattgacga gagacagcag gagctcactc
601 accaggagca ccgagtgatg ttggtgaact cgatgaacac cgtgaaagag ttgctgccag
661 ttctcatttc agctatgaag atttttgtaa caactaaaaa ctcaaaaaac caaggcatag
721 aggaagcttt aaaaaatcgc aattttactg tagaaaaaat gagtgctgaa attaatgaga
781 taattcgtgt gttacaactc acctcttggg atgaagatgc ctgggccagc aaggacactg
841 aagccatgaa gagagcattg gcctccatag actccaaact gaaccaggcc aaaggttggc
901 tccgtgaccc tagtgcctcc ccaggggatg ctggtgagca ggccatcaga cagatcttag
961 atgaagctgg aaaagttggt gaactctgtg caggcaaaga acgcagggag attctgggaa
1021 cttgcaaaat gctagggcag atgactgatc aagtggctga cctccgtgcc agaggacaag
1081 gatcctcacc ggtggccatg cagaaagctc agcaggtatc tcagggtctg gatgtgctca
1141 cagcaaaagt ggaaaatgca gctcgcaagc tggaagccat gaccaactca aagcagagca
1201 ttgcaaagaa gatcgatgct gctcagaact ggcttgcaga tccaaatggt ggaccggaag
1261 gagaagagca gattcgaggt gctttggctg aagctcggaa aatagcagaa ttatgtgatg
1321 atcctaaaga aagagatgac attctacgtt cccttgggga aatatctgct ctgacttcta
1381 aattagcaga tctacgaaga caggggaaag gagattctcc agaggctcga gccttggcca
1441 aacaggtggc cacggccctg cagaacctgc agaccaaaac caaccgggct gtggccaaca
1501 gcagaccggc caaagcagct gtacaccttg agggcaagat tgagcaagca cagcggtgga
1561 ttgataatcc cacagtggat gaccgtggag tcggtcaggc tgccatccgg gggcttgtgg
1621 ccgaagggca tcgtctggct aatgttatga tggggcctta tcggcaagat cttctcgcca
1681 agtgtgaccg agtggaccag ctgacagccc agctggctga cctggctgcc agaggggaag
1741 gggagagtcc tcaggcacga gcacttgcat ctcagctcca agactcctta aaggatctaa
1801 aagctcggat gcaggaggcc atgactcagg aagtgtcaga tgttttcagc gataccacaa
1861 ctcccatcaa gctgttggca gtggcagcca cggcgcctcc tgatgcgcct aacagggaag
1921 aggtatttga tgagagggca gctaactttg aaaaccattc aggaaagctt ggtgctacgg
1981 ccgagaaggc ggctgcggtt ggtactgcta ataaatcaac agtggaaggc attcaggcct
2041 cagtgaagac ggcccgagaa ctcacacccc aggtggtctc ggctgctcgt atcttactta
2101 ggaaccctgg aaatcaagct gcttatgaac attttgagac catgaagaac cagtggatcg
2161 ataatgttga aaaaatgaca gggctggtgg acgaagccat tgataccaaa tctctgttgg
2221 atgcttcaga agaagcaatt aaaaaagacc tggacaagtg caaggtagct atggccaaca
2281 ttcagcctca gatgctggtt gctggggcaa ccagtattgc tcgtcgggcc aaccggatcc
2341 tgctggtggc taagagggag gtggagaatt ccgaggatcc caagttccgt gaggctgtga
2401 aagctgcctc tgatgaattg agcaaaacca tctccccaat ggtgatggat gcaaaagctg
2461 tggctggaaa catttccgac cctggactgc aaaagagctt cctggactca ggatatcgga
2521 tcctgggagc tgtggccaag gtcagagaag ccttccaacc tcaggagcct gacttcccgc
2581 cgcctccacc agaccttgaa caactccgac taacagatga gcttgctcct cccaaaccac
2641 ctctgcctga aggtgaggtc cctccaccta ggcctccacc accagaggaa aaggatgaag

Figure 24. (Page 2 of 46)

2701 agttccctga gcagaaggcc ggggaggtga ttaaccagcc aatgatgatg gctgccagac
2761 agctccatga tgaagctcgc aaatggtcca gcaagggcaa tgacatcatt gcagcagcca
2821 agcgcatggc tctgctgatg gctgagatgt ctcggctggt aagaggggge agtggtacca
2881 agcgggcact cattcagtgt gccaaggaca tcgccaaggc ctcagatgag gtgactcggt
2941 tggccaagga ggttgccaag cagtgcacag ataaacggat tagaaccaac ctcttacagg
3001 tatgtgagcg aatcccaacc ataagcaccc agctcaaaat cctgtccaca gtgaaggcca
3061 ccatgctggg ccggaccaac atcagtgatg aggagtctga gcaggccaca gagatgctgg
3121 ttcacaatgc ccagaacctc atgcagtctg tgaaggagac tgtgcgggaa gctgaagctg
3181 cttcaatcaa aattcgaaca gatgctggat ttacactgcg ctgggttaga aagactccct
3241 ggtaccagta ggcacctggc tgagcctggc tggcacagaa acctctacta aaaagaagga
3301 aaatgatctg agtcccagga gctgcccaga gttgctggga gctgaaaaat cacatcctgg
3361 cctggcacat cagaaaggaa tgggggcctc ttcaaattag aagacattta tactcttttt
3421 tcatggacac tttgaaatgt gtttctgtat aaagcctgta ttctcaaaca cagttacact
3481 tgtgcaccct ctatcccaat aggcagactg ggtttctagc ccatggactt cacataagct
3541 cagaatccaa gtgaacacta gccagacact ctgctctgcc cttgttccct aggggacact
3601 tccctctgtt tctctttcct tggctcccat tcactcttcc agaatcccaa gacccagggc
3661 ccaggcaaat cagttactaa gaagaaaatt gctgtgcctc ccaaaattgt tttgagcttt
3721 ccatgttgct gccaaccata ccttccttcc ctgggctgtg ctacctgggt ccttttcaga
3781 agtgagcttt gctgctacag gggaaggtgg cctctgtgga gccccagcat atgggggcct
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4021 atcccatgaa cacactgtgt cctggtgctc tctgccactg gaagggcaga gtagccaggg
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4621 agagggcagt gtttcctttt tggtacttat tactgctaag tatttcccag cacatgaaac
4681 cttatttttt ccaaagccag aaccagatga gtaaaggagt aagaaccttg cctgaacatc
4741 cttccttccc acccatcgct gtgtgttagt tcccaacatc gaatgtgtac aacttaagtt
4801 ggtcctttac actcaggctt tcactatttc ctttaaaatg aggatgatta ttttcaaggc
4861 cctcagcata tttgtatagt tgcttgcctg atataaatgc aatattaatg cctttaaagt
4921 atgaatctat gccaaagatc acttgttgtt ttactaaaga aagattactt agaggaaata
4981 agaaaaatca tgtttgctct cccggttctt ccagtggttt gagacactgg tttacacttt
5041 atgccggatg tgcttttctc caatatcagt gctcgagaca cagtgaagca aattaaaaaa
5101 aa

Figure 24. (Page 3 of 46)

Protein Sequence of Human vinculin:

MPVFHTRTIESILEPVAQQISHLVIMHEEGEVDGKAIPDLTAPV
AAVQAAVSNLVRVGKETVQTTEDQILKRDMPPAFIKVENACTKLVQAAQMLQSDPYSV
PARDYLIDGSRGILSGTSDLLLTFDEAEVRKIIRVCKGILEYLTVAEVVETMEDLVTY
TKNLGPGMTKMAKMIDERQQELTHQEHRVMLVNSMNTVKELLPVLISAMKIFVTTKNS
KNQGIEEALKNRNFTVEKMSAEINEIIRVLQLTSWDEDAWASKDTEAMKRALASIDSK
LNQAKGWLRDPSASPGDAGEQAIRQILDEAGKVGELCAGKERREILGTCKMLGQMTDQ
VADLRARGQGSSPVAMQKAQQVSQGLDVLTAKVENAARKLEAMTNSKQSIAKKIDAAQ
NWLADPNGGPEGEEQIRGALAEARKIAELCDDPKERDDILRSLGEISALTSKLADLRR
QGKGDSPEARALAKQVATALQNLQTKTNRAVANSRPAKAAVHLEGKIEQAQRWIDNPT
VDDRGVGQAAIRGLVAEGHRLANVMMGPYRQDLLAKCDRVDQLTAQLADLAARGEGES
PQARALASQLQDSLKDLKARMQEAMTQEVSDVFSDTTTPIKLLAVAATAPPDAPNREE
VFDERAANFENHSGKLGATAEKAAAVGTANKSTVEGIQASVKTARELTPQVVSAARIL
LRNPGNQAAYEHFETMKNQWIDNVEKMTGLVDEAIDTKSLLDASEEAIKKDLDKCKVA
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ELAPPKPPLPEGEVPPPRPPPPEEKDEEFPEQKAGEVINQPMMMAARQLHDEARKWSS
KGNDIIAAAKRMALLMAEMSRLVRGGSGTKRALIQCAKDIAKASDEVTRLAKEVAKQC
TDKRIRTNLLQVCERIPTISTQLKILSTVKATMLGRTNISDEESEQATEMLVHNAQNL
MQSVKETVREAEAASIKIRTDAGFTLRWVRKTPWYQ

Figure 24. (Page 4 of 46)

M90354 Basic Transcription Factor 3 Homologue

1 aagcttttag ttccctttaa tcataaaagc cacttgctaa ctaaaactag agatagctca
61 agctatctga ttttaaaggc ttagtctcaa tgtgtccctt ccctgaaatc ccagtagagt
121 agccaattgt ctgaaacccg cttggattta gcaatgaaac acctcagtcc tggccaaacc
181 aagacagtgg gtctcaggaa acattcttca tcctaataaa ggcaaattaa ctacagttga
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481 agctggtctc acccgggact ccccaagtgc caaccctagt cccccacgca gccccttttc
541 cactcagata agatgaaaga aacaatcatg aaccaaaaac tcaccaaacg gcaagcagaa
601 gtgcacactg gtcggaaagg aactgctcac aggaaaaagg tggttcacag catctgagac
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1081 gcatcgctgg cagcaaacac tttcaccatg acaggccatg ctgagacaaa gcagctgaca
1141 gaaatgctac tcagcatcga tcataaacca gtgctgcaga tggtctgact agttcaaaga
1201 gactggctaa cactgcccaa acaatctgtg ggtggaaaag caccacttgc tactggagag
1261 gatgatgaag ttctagatct tgtggagaat tctgatgagg cttccaacaa tgaggcaaac
1321 tgaattaagt caacttctga agaagataaa acttgaagta gttactgaga gctgctgttt
1381 tatgttatga ctgcttttta aaaatgtttt tgtttacaga tcttaataaa atctagatct
1441 ctaatatttt

Figure 24. (Page 5 of 46)

J04111 Human c-jun proto oncogene

1 cccggggagg ggaccgggga acagagggcc gagaggcgtg cggcaggggg gagggtagga
61 gaaagaaggg cccgactgta ggagggcagc ggagcattac ctcatcccgt gagcctccgc
121 gggcccagag aagaatcttc tagggtggag tctccatggt gacgggcggg cccgcccccc
181 tgagagcgac gcgagccaat gggaaggcct tggggtgaca tcatgggcta tttttagggg
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361 agccagccag ccaggtcggc agtatagtcc gaactgcaaa tcttattttc ttttcacctt
421 ctctctaact gcccagagct agcgcctgtg gctcccgggc tggtggttcg ggagtgtcca
481 gagagccttg tctccagccg gccccgggag gagagccctg ctgcccaggc gctgttgaca
541 gcggcggaaa gcagcggtac cccacgcgcc cgccgggggа cgtcggcgag cggctgcagc
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661 tttgcaagcc tttcctgcgt cttaggcttc tccacggcgg taaagaccag aaggcggcgg
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961 aaccgctgcg cccgaagagc gctcagtgag tgaccgcgac ttttcaaagc cgggtagcgc
1021 gcgcgagtcg acaagtaaga gtgcgggagg catcttaatt aaccctgcgc tccctggagc
1081 gagctggtga ggagggcgca gcggggacga cagccagcgg gtgcgtgcgc tcttagagaa
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1321 tccgagagcg gaccttatgg ctacagtaac cccaagatcc tgaaacagag catgaccctg
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1441 ctcacctcgc ccgacgtggg gctgctcaag ctggcgtcgc ccgagctgga gcgcctgata
1501 atccagtcca gcaacgggca catcaccacc acgccgaccc ccacccagtt cctgtgcccc
1561 aagaacgtga cagatgagca ggaggggttc gccgagggct tcgtgcgcgc cctggccgaa
1621 ctgcacagcc agaacacgct gcccagcgtc acgtcggcgg cgcagccggt caacggggca
1681 ggcatggtgg ctcccgcggt agcctcggtg gcagggggca gcggcagcgg cggcttcagc
1741 gccagcctgc acagcgagcc gccggtctac gcaaacctca gcaacttcaa cccaggcgcg
1801 ctgagcagcg gcggcggggc gccctcctac ggcgcggccg gcctggcctt tcccgcgcaa
1861 ccccagcagc agcagcagcc gccgcaccac ctgccccagc agatgcccgt gcagcacccg
1921 cggctgcagg ccctgaagga ggagcctcag acagtgcccg agatgcccgg cgagacaccg
1981 cccctgtccc ccatcgacat ggagtcccag gagcggatca aggcggagag gaagcgcatg
2041 aggaaccgca tcgctgcctc caagtgccga aaaaggaagc tggagagaat cgcccggctg
2101 gaggaaaaag tgaaaacctt gaaagctcag aactcggagc tggcgtccac ggccaacatg
2161 ctcagggaac aggtggcaca gcttaaacag aaagtcatga accacgttaa cagtgggtgc
2221 caactcatgc taacgcagca gttgcaaaca ttttgaagag agaccgtcgg gggctgaggg
2281 gcaacgaaga aaaaaaataa cacagagaga cagacttgag aacttgacaa gttgcgacgg
2341 agagaaaaaa gaagtgtccg agaactaaag ccaagggtat ccaagttgga ctgggttcgg
2401 tctgacggcg cccccagtgt gcacgagtgg gaaggacttg gtcgcgccct cccttggcgt
2461 ggagccaggg agcggccgcc tgcgggctgc cccgctttgc ggacgggctg tccccgcgcg
2521 aacggaacgt tggactttcg ttaacattga ccaagaactg catggaccta acattcgatc
2581 tcattcagta ttaaaggggg gaggggggagg gggttacaaa ctgcaataga gactgtagat
2641 tgcttctgta gtactcctta agaacacaaa gcgggggggag ggttggggag gggcggcagg
2701 agggaggttt gtgagagcga ggctgagcct acagatgaac tctttctggc ctgctttcgt
2761 taactgtgta tgtacatata tatatttttt aatttgatta aagctgatta ctgtcaataa

Figure 24. (Page 6 of 46)

2821 acagcttcat gcctttgtaa gttatttctt gtttgtttgt ttgggtatcc tgcccagtgt
2881 tgtttgtaaa taagagattt ggagcactct gagtttacca tttgtaataa agtatataat
2941 ttttttatgt tttgtttctg aaaattccag aaaggatatt taagaaaata caataaacta
3001 ttggaaagta ctcccctaac ctcttttctg catcatctgt agatcctagt ctatctaggt
3061 ggagttgaaa gagttaagaa tgctcgataa aatcactctc agtgcttctt actattaagc
3121 agtaaaaact gttctctatt agacttagaa ataaatgtac ctgatgtacc tgatgctatg
3181 tcaggcttca tactccacgc tcccccagcg tatctatatg gaattgctta ccaaaggcta
3241 gtgcgatgtt tcaggaggct ggaggaaggg gggttgcagt ggagagggac agcccactga
3301 gaagtcaaac atttcaaagt ttggattgca tcaagtggca tgtgctgtga ccatttataa
3361 tgttagaaat tttacaatag gtgcttattc tcaaagcagg aattggtggc agattttaca
3421 aaagatgtat ccttccaatt tggaatcttc tctttgacaa ttcctagata aaaagatggc
3481 ctttgtctta tgaatattta taacagcatt ctgtcacaat aaatgtattc aaataccaat
3541 aacagatctt gaattgcttc cctttactac ttttttgttc ccaagttata tactgaagtt
3601 tttatttta gttgctgagg tt

Figure 24. (Page 7 of 46)

K00650 Human c-fos proto-oncogene

1 gcaggaacag tgctagtatt gctcgagccc gagggctgga ggttagggga tgaaggtctg
61 cttccacgct ttgcactgaa ttagggctag aattggggat gggggtaggg gcgcattcct
121 tcgggagccg aggcttaagt cctcggggtc ctgtactcga tgccgtttct cctatctctg
181 agcctcagaa ctgtcttcag tttccgtaca agggtaaaaa ggcgctctct gccccatccc
241 ccccgacctc gggaacaagg gtccgcattg aaccaggtgc gaatgttctc tctcattctg
301 cgccgttccc gcctcccctc ccccagccgc ggcccccgcc tccccccgca ctgcaccctc
361 ggtgttggct gcagcccgcg agcagttccc gtcaatccct ccccccttac acaggatgtc
421 catattagga catctgcgtc agcaggtttc cacggccttt ccctgtagcc ctgggggggag
481 ccatccccga aacccctcat cttggggggc ccacgagacc tctgagacag gaactgcgaa
541 atgctcacga gattaggaca cgcgccaagg cgggggcagg gagctgcgag cgctggggac
601 gcagccgggc ggccgcagaa gcgcccaggc ccgcgcgcca cccctctggc gccaccgtgg
661 ttgagcccgt gacgtttaca ctcattcata aaacgcttgt tataaaagca gtggctgcgg
721 cgcctcgtac tccaaccgca tctgcagcga gcaactgaga agccaagact gagccggcgg
781 ccgcggcgca gcgaacgagc agtgaccgtg ctcctaccca gctctgcttc acagcgccca
841 cctgtctccg cccctcggcc cctcgcccgg ctttgcctaa ccgccacgat gatgttctcg
901 ggcttcaacg cagactacga ggcgtcatcc tcccgctgca gcagcgcgtc cccggccggg
961 gatagcctct cttactacca ctcacccgca gactccttct ccagcatggg ctcgcctgtc
1021 aacgcgcagg taaggctggc ttcccgtcgc cgcggggccg ggggcttggg gtcgcggagg
1081 aggagacacc gggcgggacg ctccagtaga tgagtagggg gctcccttgt gcctggaggg
1141 aggctgccgt ggccggagcg gtgccggctc gggggctcgg gacttgctct gagcgcacgc
1201 acgcttgcca tagtaagaat tggttccccc ttcgggaggc aggttcgttc tgagcaacct
1261 ctggtctgca ctccaggacg gatctctgac attagctgga gcagacgtgt cccaagcaca
1321 aactcgctaa ctagagcctg gcttcttcgg ggaggtggca gaaagcggca atccccccctc
1381 ccccggcagc ctggagcacg gaggagggat gagggaggag ggtgcagcgg gcgggtgtgt
1441 aaggcagttt cattgataaa aagcgagttc attctggaga ctccggagcg gcgcctgcgt
1501 cagcgcagac gtcagggata tttataacaa acccccttc aagcaagtga tgctgaaggg
1561 ataacgggaa cgcagcggca ggatggaaga gacaggcact gcgctgcgga atgcctggga
1621 ggaaaagggg gagacctttc atccaggatg agggacattt aagatgaaat gtccgtggca
1681 ggatcgtttc tcttcactgc tgcatgcggc actgggaact cgccccacct gtgtccggaa
1741 cctgctcgct cacgtcggct ttcccttct gttttgttct aggacttctg cacggacctg
1801 gccgtctcca gtgccaactt cattcccacg gtcactgcca tctcgaccag tccggacctg
1861 cagtggctgg tgcagcccgc cctcgtctcc tctgtggccc catcgcagac cagagccccc
1921 cacccttccg gagtccccgc cccctccgct ggggcttact ccagggctgg cgttgtgaag
1981 accatgacag gaggccgagc gcagagcatt ggcaggaggg gcaaggtgga acaggtgagg
2041 aactctagcg tactcttcct gggaatgtgg gggctgggtg ggaagcagcc ccggagatgc
2101 aggagcccag tacagaggat gaagccactg atggggctgg ctgcacatcc gtaactggga
2161 gccctggctc caagcccatt ccatcccaac tcagactctg agtctcaccc taagaagtac
2221 tctcatagtt tcttccctaa gtttcttacc gcatgctttc agactgggct cttctttgtt
2281 ctcttgctga ggatcttatt ttaaatgcaa gtcacaccta ttctgcaact gcaggtcaga
2341 aatggtttca cagtggggtg ccaggaagca gggaagctgc aggagccagt tctactgggg
2401 tgggtgaatg gaggtgatgg cagacacttt tactgaatgt cggtcttttt ttgtgattat
2461 tctagttatc tccagaagaa gaagagaaaa ggagaatccg aagggaaagg aataagatgg
2521 ctgcagccaa atgccgcaac cggaggaggg agctgactga tacactccaa gcggtaggta
2581 ctctgtgggt tgctcctttt taaaacttaa gggaaagttg gagattgagc ataagggccc
2641 ttgagtaaga ctgtgtctta tgctttcctt tatccctctg tatacaggag acagaccaac
2701 tagaagatga gaagtctgct ttgcagaccg agattgccaa cctgctgaag gagaaggaaa
2761 aactagagtt catcctggca gctcaccgac ctgcctgcaa gatccctgat gacctgggct

Figure 24. (Page 8 of 46)

2821 tcccagaaga gatgtctgtg gcttcccttg atctgactgg gggcctgcca gaggttgcca
2881 ccccggagtc tgaggaggcc ttcaccctgc ctctcctcaa tgaccctgag cccaagccct
2941 cagtggaacc tgtcaagagc atcagcagca tggagctgaa gaccgagccc tttgatgact
3001 tcctgttccc agcatcatcc aggcccagtg gctctgagac agcccgctcc gtgccagaca
3061 tggacctatc tgggtccttc tatgcagcag actgggagcc tctgcacagt ggctccctgg
3121 ggatggggcc catggccaca gagctggagc ccctgtgcac tccggtggtc acctgtactc
3181 ccagctgcac tgcttacacg tcttccttcg tcttcaccta ccccgaggct gactccttcc
3241 ccagctgtgc agctgcccac cgcaagggca gcagcagcaa tgagccttcc tctgactcgc
3301 tcagctcacc cacgctgctg gccctgtgag ggggcaggga aggggaggca gccggcaccc
3361 acaagtgcca ctgcccgagc tggtgcatta cagagaggag aaacacatct tccctagagg
3421 gttcctgtag acctagggag gaccttatct gtgcgtgaaa cacaccaggc tgtgggcctc
3481 aaggacttga aagcatccat gtgtggactc aagtccttac ctcttccgga gatgtagcaa
3541 aacgcatgga gtgtgtattg ttcccagtga cacttcagag agctggtagt tagtagcatg
3601 ttgagccagg cctgggtctg tgtctctttt ctctttctcc ttagtcttct catagcatta
3661 actaatctat tgggttcatt attggaatta acctggtgct ggatattttc aaattgtatc
3721 tagtgcagct gattttaaca ataactactg tgttcctggc aatagtgtgt tctgattaga
3781 aatgaccaat attatactaa gaaaagatac gactttattt tctggtagat agaaataaat
3841 agctatatcc atgtactgta gtttttcttc aacatcaatg ttcattgtaa tgttactgat
3901 catgcattgt tgaggtggtc tgaatgttct gacattaaca gttttccatg aaaacgtttt
3961 attgtgtttt taatttattt attaagatgg attctcagat atttatattt ttatttttatt
4021 tttttctacc ttgaggtctt ttgacatgtg gaaagtgaat ttgaatgaaa aatttaagca
4081 ttgtttgctt attgttccaa gacattgtca ataaaagcat ttaagttgaa tgcgaccaac
4141 cttgtgctct tttcattctg gaagtcttgt aagtttctga aaggtattat tggagaccag
4201 tttgtcaaga agggtagctg ctggaggggg acacaccctc tgtctgatcc cttatcaaag
4261 aggacaagga aactatagag ctgattttag aatattttac aaatacatgc cttccattgg
4321 aatgctaaga ttttctactg cttctgggga cgggaaaccg ctgtgtaaca gcttttgtgg
4381 gaatacattt tttctgtttc agtactcgca gggggaaata tttaaatttt gttgtgctaa
4441 tattaaattc agatgttttg atcttaaagg aacccttaa gcaaacagaa cctagctttg
4501 tacagactat tttaactttt tattctcaca aaatcacgtg gagggttatt ctacttcaaa
4561 gatgagcaaa ttgaagaatg gttagaataa acaactttct tgatattccg ttatcggcat
4621 tagaatcttc ctgctcgtta tcgtatccag caggctgaac tgcctcttga tacttggtta
4681 aaaaaaattt tcaggccggg cgcggtggcc catgcctgta atcctagcac tttgggaggc
4741 cgaggcaggc ggatcacctg aggtcgggag ttcgagacca gcctgaccaa catggagaaa
4801 ccccgtcttt actaaaaata caaaattagc ctggtgtggt ggtgcatgcc tgtaatccta
4861 gctacttgag aggctgagac aggaaaatca cttgaactcg ggaggcggat gttgcagcga
4921 actgagattg cgccattgca ctccagcctg ggcaacaaga ttgaaactct gtttaaaaaa
4981 aaaagttttc actaatgtgt acatttttt gtactctttt attctcgaaa gggaaggagg
5041 gctattgccc tatcccttat taataaatgc attgtggttt ctggtttctc taataccata
5101 tgcccttcat tcagtttata gtgggcggaa gtgggggaga aaaagttgct cagaaatcaa
5161 aagatatctc aaacagcaca aataatggct gatcgttctg caaacaaaaa gttacataat
5221 agctcaagaa ggagaagtca acatgactct gaacaagctt taacttagaa actttatcat
5281 cttaaggaag aacgtgacct ttgtccagga cgtctctggt aatggggcac ttacacacac
5341 atgcacacgt acaaaccaca gggaaaggag accgcccttc tgcctctgct cgcgagtatc
5401 acgcaggcac catgcactat gttttcacac acactgggtg gaagaagagc ttcagcgcca
5461 gtcttctaat gctttggtga taatgaaaat cactgggtgc ttatggggtg tcatattcaa
5521 tcgagttaaa agttttaatt caaaatgaca gttttactga ggttgatgtt ctcgtctatg
5581 atatctctgc ccctcccata aaaatggaca tttaaaagca acttaccgct ctttagatca
5641 ctcctatatc acacaccact tggggtgctg tttctgctag acttgtgatg acagtggcct
5701 taggatccct gtttgctgtt caaagggcaa atattttata gcctttaaat atacctaaac

Figure 24. (Page 9 of 46)

5761 taaatacaga attaatataa ctaacaaaca cctggtctga aataacaagg tgatctaccc
5821 tggaaggaac ccagctggtg ggccaggagc ggtggctcac acctgtaatt ccagcacttt
5881 gggaggctga gacaggagga tcactggagt ccaggagttt gagaccagcc tgggcaacat
5941 ggcaaaaccc agtgtgcttc tgttgtccca gctacactac tcaggaggct gaggcaggag
6001 tatgacttga gcctgggagg gggaggttgc agagaactga tattgcacca ccactgcact
6061 ccagcctggg tgacacagca aaaccctatc tcaaaaaaaa aaaaaaaaaa aaggaaccca
6121 gctggttcct gtaggtgtgc aataataaca accagaggaa gaaaaggaag acgatttccc
6181 agatgaagaa gggcagctgg accttcggac

Figure 24. (Page 10 of 46)

NM_080422 Homo Sapiens Protein Tyrosine Phosphatase, non-receptor type 2

1 gctcgggcgc cgagtctgcg cgctgacgtc cgacgctcca ggtactttcc ccacggccga
61 cagggcttgg cgtgggggcg gggcgcggcg cgcagcgcgc atgcgccgca gcgccagcgc
121 tctccccgga tcgtgcgggg cctgagcctc tccgccggcg caggctctgc tcgcgccagc
181 tcgctcccgc agccatgccc accaccatcg agcgggagtt cgaagagttg gatactcagc
241 gtcgctggca gccgctgtac ttggaaattc gaaatgagtc ccatgactat cctcatagag
301 tggccaagtt tccagaaaac agaaatcgaa acagatacag agatgtaagc ccatatgatc
361 acagtcgtgt taaactgcaa aatgctgaga atgattatat taatgccagt ttagttgaca
421 tagaagaggc acaaaggagt tacatcttaa cacagggtcc acttcctaac acatgctgcc
481 atttctggct tatggtttgg cagcagaaga ccaaagcagt tgtcatgctg aaccgcattg
541 tggagaaaga atcggttaaa tgtgcacagt actggccaac agatgaccaa gagatgctgt
601 ttaaagaaac aggattcagt gtgaagctct tgtcagaaga tgtgaagtcg tattatacag
661 tacatctact acaattagaa aatatcaata gtggtgaaac cagaacaata tctcactttc
721 attatactac ctggccagat tttggagtcc ctgaatcacc agcttcattt ctcaatttct
781 tgtttaaagt gagagaatct ggctccttga accctgacca tgggcctgcg gtgatccact
841 gtagtgcagg cattgggcgc tctggcacct tctctctggt agacacttgt cttgttttga
901 tggaaaaagg agatgatatt aacataaaac aagtgttact gaacatgaga aaataccgaa
961 tgggtcttat tcagacccca gatcaactga gattctcata catggctata atagaaggag
1021 caaaatgtat aaagggagat tctagtatac agaaacgatg gaaagaactt tctaaggaag
1081 acttatctcc tgcctttgat cattcaccaa acaaaataat gactgaaaaa tacaatggga
1141 acagaatagg tctagaagaa gaaaaactga caggtgaccg atgtacagga ctttcctcta
1201 aaatgcaaga tacaatggag gagaacagtg agagtgctct acggaaacgt attcgagagg
1261 acagaaaggc caccacagct cagaaggtgc agcagatgaa acagaggcta aatgagaatg
1321 aacgaaaaag aaaaaggcca agattgacag acacctaata ttcatgactt gagaatattc
1381 tgcagctata aattttgaac cattgatgtg caaagcaaga cctgaagccc actccggaaa
1441 ctaaagtgag gctcgctaac cctctagatt gcctcacagt tgtttgttta caaagtaaac
1501 tttacatcca ggggatgaag agcacccacc agcagaagac tttgcagaac ctttaattgg
1561 atgtgttaag tgtttttaat gagtgtatga aatgtagaaa gatgtacaag aaataaatta
1621 ggagagatta ctttgtattg tactgccatt cctactgtat ttttatactt tttggcagca
1681 ttaaatattt ttgttaaata aaaaaaaaaa aaaa

Figure 24. (Page 11 of 46)

M68520 Human cdc2-related protein kinase

1 ggaggcggca acattgtttc aagttggcca aattgacaag agcgagaggt atactgcgtt
61 ccatcccgac ccgggccacg gtactgggcc ctgtttcccc ctcctcggcc cccgagagcc
121 agggtccgcc ttctgcaggg ttcccaggcc cccgctccag ggccgggctg acccgactcg
181 ctggcgcttc atggagaact tccaaaaggt ggaaaagatc ggagagggca cgtacggagt
241 tgtgtacaaa gccagaaaca agttgacggg agaggtggtg gcgcttaaga aaatccgcct
301 ggacactgag actgagggtg tgcccagtac tgccatccga gagatctctc tgcttaagga
361 gcttaaccat cctaatattg tcaagctgct ggatgtcatt cacacagaaa ataaactcta
421 cctggttttt gaatttctgc accaagatct caagaaattc atggatgcct ctgctctcac
481 tggcattcct cttcccctca tcaagagcta tctgttccag ctgctccagg gcctagcttt
541 ctgccattct catcgggtcc tccaccgaga ccttaaacct cagaatctgc ttattaacac
601 agagggggcc atcaagctag cagactttgg actagccaga gcttttggag tccctgttcg
661 tacttacacc catgaggtgg tgaccctgtg gtaccgagct cctgaaatcc tcctgggctg
721 caaatattat tccacagctg tggacatctg gagcctgggc tgcatctttg ctgagatggt
781 gactcgccgg gccctattcc ctggagattc tgagattgac cagctcttcc ggatctttcg
841 gactctgggg accccagatg aggtggtgtg gccaggagtt acttctatgc ctgattacaa
901 gccaagtttc cccaagtggg cccggcaaga ttttagtaaa gttgtacctc ccctggatga
961 agatggacgg agcttgttat cgcaaatgct gcactacgac cctaacaagc ggatttcggc
1021 caaggcagcc ctggctcacc ctttcttcca ggatgtgacc aagccagtac cccatcttcg
1081 actctgatag ccttcttgaa gccccccagcc ctaatctcac cctctcctcc agtgtgggct
1141 tgaccaggct tgcgcttggg ctatttggac tcaggtgggc cctctgaact tgccttaaac
1201 actcaccttc tagtcttggc cagccaactc tgggaataca ggggtgaaag gggggaacca
1261 gtgaaaatga aaggaagttt cagtattaga tgcacttaag ttagcctcca ccacccttc
1321 ccccttctct tagttattgc tgaagagggt tggtataaaa ataatttaa aaaagccttc
1381 ctacacgtta gatttgccgt accaatctct gaatgcccca taattattat ttccagtgtt
1441 tgggatgacc aggatcccaa gcctcctgct gccacaatgt ttataaaggc caaatgatag
1501 cgggggctaa gttggtgctt ttgagaacca agtaaaacaa aaccactggg aggagtctat
1561 tttaaagaat tcggttgaaa aaaatagatc caatcagttt ataccctagt tagtgttttg
1621 cctcacctaa taggctggga gactgaagac tcagcccggg tggctgcaga aaaatgattg
1681 gccccagtcc ccttgtttgt cccttctaca ggcatgagga atctgggagg ccctgagaca
1741 gggattgtgc ttcattccaa tctattgctt caccatggcc ttatgaggca ggtgagagat
1801 gtttgaattt ttctcttcct tttagtattc ttagttgttc agttgccaag gatccctgat
1861 cccattttcc tctgacgtcc acctcctacc ccataggagt tagaagttag ggtttaggca
1921 tcattttgag aatgctgaca ctttttcagg gctgtgattg agtgagggca tgggtaaaaa
1981 tatttcttta aaagaaggat gaacaattat atttatattt caggttatat ccaatagtag
2041 agttggcttt ttttttttt ttttggtcat agtgggtgga tttgttgcca tgtgcacctt
2101 ggggttttgt aatgacagtg ctaaaaaaaa agcatttttt ttttatgatt tgtctctgtc
2161 acccttgtcc ttgagtgctc ttgctattaa cgttatttgt aatttagttt gta

Figure 24. (Page 12 of 46)

M74091 Human Cyclin C

1 gagcgcggtt accggacggg ctgggtctat ggtcgctccg cggccgctcc gccgcgtggt
61 gctttttat cagggcaagc tgtgttccat ggcagggaac ttttggcaga gctcccacta
121 tttgcaatgg attttggata aacaagatct gttgaaggag cgccaaaagg atttaaagtt
181 tctctcagag gaagaatatt ggaagttaca aatatttttt acaaatgtta tccaagcatt
241 aggtgaacat cttaaattaa gacaacaagt tattgccact gctacggtat atttcaagag
301 attctatgcc aggtattctc tgaaaagtat agatcctgta ttaatggctc ctacatgtgt
361 gtttttggca tccaaagtag aggaatttgg agtagtttca aatacaagat tgattgctgc
421 tgctacttct gtattaaaaa ctagattttc atatgccttt ccaaaggaat ttccttatag
481 gatgaatcat atattagaat gtgaattcta tctgttagaa ctaatggatt gttgcttgat
541 agtgtatcat ccttatagac ctttgctcca gtatgtgcag gacatgggcc aagaagacat
601 gttgcttccc cttgcatgga ggatagtgaa tgatacctac agaacggatc tttgcctact
661 gtatcctcct ttcatgatag ctttagcttg cctacatgta gcctgtgttg tacagcagaa
721 agatgccagg caatggtttg ctgagctttc tgtggatatg gaaaagattt tggaaataat
781 cagggttatt ttaaaactat atgagcagtg gaagaatttc gatgagagaa aagagatggc
841 aaccattctt agtaagatgc caaaaccaaa accacctcca aacagtgaag gagagcaggg
901 tccaaatgga agtcagaact ctagctacag ccaatcttaa aacattccga agaattccat
961 agtggaccac ttggaaataa accattggac agatttcagt aatgtcttca gtggaacaca
1021 aatgaaaatg aatagcttgt ttctgtcaag catattggaa agtgatttta tttttgcaaa
1081 tagtttttct ttaatatgat tctagtacat aattgattga ttaaatctct tgattataaa
1141 tgtttggaaa ggttctaagg ggacctacag acagacatac atagacattt caaaattaat
1201 agcttttgat tagtataata tttcttaatt tggataataa aaattgtagc tttttattaa
1261 gccaggaaac atgaagcata atttgtttaa aattctcttt ggtcattgag ggaccaaaaa
1321 aggacgtaaa atttacagtc aatctatgag ggtttttttc cctccataag tttaacttta
1381 aaactgtatt taaggaatca aatcttacaa aatcctggaa gattttggta atgatgttga
1441 taatttcagg gaaattaatc aagtaccgta tattgattta aaagtgtatt ttattcagta
1501 gtttgagg

Figure 24. (Page 13 of 46)

U60325 Human DNA polymerase gamma

1 aggatttggg gtggaaggca ggcatggtca acccatgtca ctgacaggag agcagagaca
61 gacgtgtctc tctccacgtc ttccagccag taaaagaagc caagctggag cccaaagcca
121 ggtgttctga ctcccagcgt gggggtccct gcaccaacca tgagccgcct gctctggagg
181 aaggtggccg gcgccaccgt cgggccaggg ccggttccag ctccggggcg ctgggtctcc
241 agctccgtcc ccgcgtccga ccccagcgac gggcagcggc ggcggcagca gcagcagcag
301 cagcagcagc agcagcaaca gcagcctcag cagccgcaag tgctatcctc ggagggcggg
361 cagctgcggc acaacccatt ggacatccag atgctctcga gagggctgca cgagcaaatc
421 ttcgggcaag gaggggagat gcctggcgag gccgcggtgc gccgcagcgt cgagcacctg
481 cagaagcacg ggctctgggg gcagccagcc gtgcccttgc ccgacgtgga gctgcgcctg
541 ccgcccctct acggggacaa cctggaccag cacttccgcc tcctggccca gaagcagagc
601 ctgccctacc tggaggcggc caacttgctg ttgcaggccc agctgccccc gaagcccccg
661 gcttgggcct gggcggaggg ctggacccgg tacggccccg agggggaggc cgtacccgtg
721 gccatccccg aggagcgggc cctggtgttc gacgtggagg tctgcttggc agagggaact
781 tgccccacat tggcggtggc catatccccc tcggcctggt attcctggtg cagccagcgg
841 ctggtggaag agcgttactc ttggaccagc cagctgtcgc cggctgacct catccccctg
901 gaggtcccta ctggtgccag cagccccacc cagagagact ggcaggagca gttagtggtg
961 gggcacaatg tttcctttga ccgagctcat atcagggagc agtacctgat ccagggttcc
1021 cgcatgcgtt tcctggacac catgagcatg cacatggcca tctcagggct aagcagcttc
1081 cagcgcagtc tgtggatagc agccaagcag ggcaaacaca aggtccagcc ccccacaaag
1141 caaggccaga agtcccagag gaaagccaga agaggcccag cgatctcatc ctgggactgg
1201 ctggacatca gcagtgtcaa cagtctggca gaggtgcaca gactttatgt agggggggcct
1261 cccttagaga aggagcctcg agaactgttt gtgaagggca ccatgaagga cattcgtgag
1321 aacttccagg acctgatgca gtactgtgcc caggacgtgt gggccaccca tgaggttttc
1381 cagcagcagc taccgctctt cttggagagg tgtccccacc cagtgactct ggccggcatg
1441 ctggagatgg gtgtctccta cctgcctgtc aaccagaact gggagcgtta cctggcagag
1501 gcacagggca cttatgagga gctccagcgg gagatgaaga agtcgttgat ggatctggcc
1561 aatgatgcct gccagctgct ctcaggagag aggtacaaag aagacccctg gctctgggac
1621 ctggagtggg acctgcaaga atttaagcag aagaaagcta agaaggtgaa gaaggaacca
1681 gccacagcca gcaagttgcc catcgagggg gctggggccc ctggtgatcc catggatcag
1741 gaagacctcg gcccctgcag tgaggaggag gagtttcaac aagatgtcat ggcccgcgcc
1801 tgcttgcaga agctgaaggg gaccacagag ctcctgccca agcggcccca gcaccttcct
1861 ggacaccctg gatggtaccg gaagctctgc ccccggctag acgaccctgc atggaccccg
1921 ggccccagcc tcctcagcct gcagatgcgg gtcacaccta aactcatggc acttacctgg
1981 gatggcttcc ctctgcacta ctcagagcgt catggctggg gctacttggt gcctgggcgg
2041 cgggacaacc tggccaagct gccgacaggt accaccctgg agtcagctgg ggtggtctgc
2101 ccctacagag ccatcgagtc cctgtacagg aagcactgtc tcgaacaggg gaagcagcag
2161 ctgatgcccc aggaggccgg cctggcggag gagttcctgc tcactgacaa tagtgccata
2221 tggcaaacgg tagaagaact ggattactta gaagtggagg ctgaggccaa gatggagaac
2281 ttgcgagctg cagtgccagg tcaacccta gctctgactg cccgtggtgg ccccaaggac
2341 acccagccca gctatcacca tggcaatgga ccttacaacg acgtggacat ccctggctgc
2401 tggtttttca agctgcctca caaggatggt aatagctgta atgtgggaag ccccttgcc
2461 aaggacttcc tgcccaagat ggaggatggc accctgcagg ctggcccagg aggtgccagt
2521 gggccccgtg ctctggaaat caacaaaatg atttctttct ggaggaacgc ccataaacgt
2581 atcagctccc agatggtggt gtggctgccc aggtcagctc tgccccgtgc tgtgatcagg
2641 caccccgact atgatgagga aggcctctat ggggccatcc tgccccaagt ggtgactgcc
2701 ggcaccatca ctcgccgggc tgtggagccc acatggctca ccgccagcaa tgcccggcct
2761 gaccgagtag gcagtgagtt gaaagccatg gtgcaggccc cacctggcta caccttgtg

Figure 24. (Page 14 of 46)

2821 ggtgctgatg tggactccca agagctgtgg attgcagctg tgcttggaga cgcccacttt
2881 gccggcatgc atggctgcac agcctttggg tggatgacac tgcagggcag gaagagcagg
2941 ggcactgatc tacacagtaa gacagccact actgtgggca tcagccgtga gcatgccaaa
3001 atcttcaact acggccgcat ctatggtgct gggcagccct ttgctgagcg cttactaatg
3061 cagtttaacc accggctcac acagcaggag gcagctgaga aggcccagca gatgtacgct
3121 gccaccaagg gcctccgctg gtatcggctg tcggatgagg gcgagtggct ggtgagggag
3181 ttgaacctcc cagtggacag gactgagggt ggctggattt ccctgcagga tctgcgcaag
3241 gtccagagag aaactgcaag gaagtcacag tggaagaagt gggaggtggt tgctgaacgg
3301 gcatggaagg ggggcacaga gtcagaaatg ttcaataagc ttgagagcat tgctacgtct
3361 gacataccac gtaccccggt gctgggctgc tgcatcagcc gagccctgga gccctcggct
3421 gtccaggaag agtttatgac cagccgtgtg aattgggtgg tacagagctc tgctgttgac
3481 tacttacacc tcatgcttgt ggccatgaag tggctgtttg aagagtttgc catagatggg
3541 cgcttctgca tcagcatcca tgacgaggtt cgctacctgg tgcgggagga ggaccgctac
3601 cgcgctgccc tggccttgca gatcaccaac ctcttgacca ggtgcatgtt tgcctacaag
3661 ctgggtctga atgacttgcc ccagtcagtc gccttttca gtgcagtcga tattgaccgg
3721 tgcctcagga aggaagtgac catggattgt aaaaccccct ccaacccaac tgggatggaa
3781 aggagatacg ggattcccca gggtgaagcg ctggatattt accagataat tgaactcacc
3841 aaaggctcct tggaaaaacg aagccagcct ggaccatagc actgcctgga ggctctgtat
3901 ttgctcccgt ggagcttcat cggggtggtg caggctccca aactcaggct ttcagctgtg
3961 ctttttgcaa aagggcttgc taaggccagc catttttcag tagcaggacc tgccaagaag
4021 attccttcta actgaaggtg cagttgaatt cagtgggttc agaaccaaga tgccaacatc
4081 ggtgtggact acaggacaag gggcattgtt gcttgttggg taaaaatgaa gcagaagccc
4141 caaagttcac attaactcag gcatttcatt tatttttcc ttttcttctt ggctggttct
4201 ttgttctgtc ccccatgctc tgatgcagtg ccctagaagg ggaaagaatt aatgctctaa
4261 cgtgataaac ctgctccaag gcagtggaaa taaaaagaag gaaaaaaaaa aaaaaaaaaa

Figure 24. (Page 15 of 46)

X52479 Protein Kinase C alpha

1 ggagcaagag gtggttgggg ggggaccatg gctgacgttt tcccgggcaa cgactccacg
61 gcgtctcagg acgtggccaa ccgcttcgcc cgcaaagggg cgctgaggca gaagaacgtg
121 cacgaggtga aggaccacaa attcatcgcg cgcttcttca agcagcccac cttctgcagc
181 cactgcaccg acttcatctg ggggtttggg aaacaaggct tccagtgcca agtttgctgt
241 tttgtggtcc acaagaggtg ccatgaattt gttacttttt cttgtccggg tgcggataag
301 ggacccgaca ctgatgaccc caggagcaag cacaagttca aaatccacac ttacggaagc
361 cccaccttct gcgatcactg tgggtcactg ctctatggac ttatccatca agggatgaaa
421 tgtgacacct gcgatatgaa cgttcacaag caatgcgtca tcaatgtccc cagcctctgc
481 ggaatggatc acactgagaa gaggggcgg atttacctaa aggctgaggt tgctgatgaa
541 aagctccatg tcacagtacg agatgcaaaa aatctaatcc ctatggatcc aaacgggctt
601 tcagatcctt atgtgaagct gaaacttatt cctgatccca agaatgaaag caagcaaaaa
661 accaaaacca tccgctccac actaaatccg cagtggaatg agtcctttac attcaaattg
721 aaaccttcag acaaagaccg acgactgtct gtagaaatct gggactggga tcgaacaaca
781 aggaatgact tcatgggatc cctttccttt ggagtttcgg agctgatgaa gatgccggcc
841 agtggatggt acaagttgct taaccaagaa gaaggtgagt actacaacgt acccattccg
901 gaaggggacg aggaaggaaa catggaactc aggcagaaat tcgagaaagc caaacttggc
961 cctgctggca acaaagtcat cagtccctct gaagacagga aacaaccttc caacaacctt
1021 gaccgagtga aactcacgga cttcaatttc ctcatggtgt tgggaaaggg gagttttgga
1081 aaggtgatgc ttgccgacag gaagggcaca gaagaactgt atgcaatcaa aatcctgaag
1141 aaggatgtgg tgattcagga tgatgacgtg gagtgcacca tggtagaaaa gcgagtcttg
1201 gccctgcttg acaaaccccc gttcttgacg cagctgcact cctgcttcca gacagtggat
1261 cggctgtact tcgtcatgga atatgtcaac ggtggggacc tcatgtacca cattcagcaa
1321 gtaggaaaat ttaaggaacc acaagcagta ttctatgcgg cagagatttc catcggattg
1381 ttctttcttc ataaaagagg aatcatttat agggatctga agttagataa cgtcatgttg
1441 gattcagaag gacatatcaa aattgctgac tttgggatgt gcaaggaaca catgatggat
1501 ggagtcacga ccaggacctt ctgtgggact ccagattata tcgccccaga gataatcgct
1561 tatcagccgt atggaaaatc tgtggactgg tgggcctatg gcgtcctgtt gtatgaaatg
1621 cttgccgggc agcctccatt tgatggtgaa gatgaagacg agctatttca gtctatcatg
1681 gagcacaacg tttcctatcc aaaatccttg tccaaggagg ctgtttctat ctgcaaagga
1741 ctgatgacca aacacccagc caagcggctg ggctgtgggc ctgaggggga gagggacgtg
1801 agagagcatg ccttcttccg gaggatcgac tgggaaaaac tggagaacag ggagatccag
1861 ccaccattca agcccaaagt gtgtggcaaa ggagcagaga actttgacaa gttcttcaca
1921 cgaggacagc ccgtcttaac accacctgat cagctggtta ttgctaacat agaccagtct
1981 gattttgaag ggttctcgta tgtcaacccc cagtttgtgc accccatctt acagagtgca
2041 gtatgaaact caccagcgag aacaaacacc tccccagccc ccagccctcc ccgcagtgga
2101 agtgaatcct taaccctaaa attttaaggc cacggcttgt gtctgattcc atatggaggc
2161 ctgaaaattg tagggttatt agtccaaatg tgatcaactg ttcagggtct ctctcttaca
2221 accaagaaca ttatcttagt ggaag

Figure 24. (Page 16 of 46)

D00017 Lipocortin II/Annexin A2

1 catttgggga cgctctcagc tctcggcgca cggcccagct tccttcaaaa tgtctactgt
61 tcacgaaatc ctgtgcaagc tcagcttgga gggtgatcac tctacacccc caagtgcata
121 tgggtctgtc aaagcctata ctaactttga tgctgagcgg gatgctttga acattgaaac
181 agccatcaag accaaaggtg tggatgaggt caccattgtc aacattttga ccaaccgcag
241 caatgcacag agacaggata ttgccttcgc ctaccagaga aggaccaaaa aggaacttgc
301 atcagcactg aagtcagcct tatctggcca cctggagacg gtgattttgg gcctattgaa
361 gacacctgct cagtatgacg cttctgagct aaaagcttcc atgaaggggc tgggaaccga
421 cgaggactct ctcattgaga tcatctgctc cagaaccaac caggagctgc aggaaattaa
481 cagagtctac aaggaaatgt acaagactga tctggagaag gacattattt cggacacatc
541 tggtgacttc cgcaagctga tggttgccct ggcaaagggt agaagagcag aggatggctc
601 tgtcattgat tatgaactga ttgaccaaga tgctcgggat ctctatgacg ctggagtgaa
661 gaggaaagga actgatgttc ccaagtggat cagcatcatg accgagcgga gcgtgcccca
721 cctccagaaa gtatttgata ggtacaagag ttacagccct tatgacatgt tggaaagcat
781 caggaaagag gttaaaggag acctggaaaa tgctttcctg aacctggttc agtgcattca
841 gaacaagccc ctgtattttg ctgatcggct gtatgactcc atgaagggca aggggacgcg
901 agataaggtc ctgatcagaa tcatggtctc ccgcagtgaa gtggacatgt tgaaaattag
961 gtctgaattc aagagaaagt acggcaagtc cctgtactat tatatccagc aagacactaa
1021 gggcgactac cagaaagcgc tgctgtacct gtgtggtgga gatgactgaa gcccgacacg
1081 gcctgagcgt ccagaaatgg tgctcaccat gcttccagct aacaggtcta gaaaaccagc
1141 ttgcgaataa cagtccccgt ggccatccct gtgagggtga cgttagcatt acccccaacc
1201 tcattttagt tgcctaagca ttgcctggcc ttcctgtcta gtctctcctg taagccaaag
1261 aaatgaacat tccaaggagt tggaagtgaa gtctatgatg tgaaacactt tgcctcctgt
1321 gtactgtgtc ataaacagat gaataaactg aatttgtact tt

Figure 24. (Page 17 of 46)

AF531293 Histone H2b, member R

1 aagagcgagt cttggcctta gcgcgggctt tgcctccctg cttgccacgt ccagacatag
61 cgagcgcaac tcactacgag caaccacaaa gtgaacggga aaggcggcgc ttttataaa
121 cactattggg cgcgaaaaag aagacgtgtt gttggttagg gctgcagttt aatttcaacc
181 aatagtagtg cgtcttctgg atttgcgaat cctgattggg cagacctgac ctctgacgtt
241 accctgaata actaccaatc agacacaaga cttcaactct tcaccttatt tgcataagcg
301 attctatata aaagcgcctt gtcataccct gctcacgctg tttttccttt tcgttggcgc
361 tttatagcta cacagtgcta tgccagagcc agcgaagtct gctcccgccc cgaaaaaggg
421 ctccaagaag gcggtgacta aggcgcagaa gaaagacggc aagaagcgca agcgcagccg
481 caaggagagc tattccatct atgtgtacaa ggttctgaag caggtccacc ctgacaccgg
541 catttcgtcc aaggccatgg gcatcatgaa ttcgtttgtg aacgacattt tcgagcgcat
601 cgcaggtgag gcttcccgcc tggcgcatta caacaagcgc tcgaccatca cctccaggga
661 gatccagacg gccgtgcgcc tgctgctgcc tggggagttg gccaagcacg ccgtgtccga
721 gggtactaag gccgtcacca agtacaccag cgctaagtaa acagtgagtt ggttgcaaac
781 tctcaaccct aacggctctt ttaagagcca cccatgttct caaagaaaga gctggtgctt
841 gtattcctcc tctgctggcc actgacaaac ccttgtaact tgctactgtg ttttttggtc
901 tgaagtagag cagttattta actaatcctt agtgactttt ttttttaga tctgccattc
961 taatcttaga gttaagtaag gagatgggaa attttctatt ataagttcga aaccaattaa
1021 aatacgttag aaaccaatta aaatactcgt cggtcccccg tcggttagtg atttggaaca
1081 gtgccaagtt gcagcggttg tcagtttgaa tttgcccggg caacgcccgc ccttcct

Figure 24. (Page 18 of 46)

NM_001657 Homo Sapiens amphiregulin

1 agacgttcgc acacctgggt gccagcgccc cagaggtccc gggacagccc gaggcgccgc
61 gcccgccgcc ccgagctccc caagccttcg agagcggcgc acactcccgg tctccactcg
121 ctcttccaac acccgctcgt tttggcggca gctcgtgtcc cagagaccga gttgccccag
181 agaccgagac gccgccgctg cgaaggacca atgagagccc cgctgctacc gccggcgccg
241 gtggtgctgt cgctcttgat actcggctca ggccattatg ctgctggatt ggacctcaat
301 gacacctact ctgggaagcg tgaaccattt tctggggacc acagtgctga tggatttgag
361 gttacctcaa gaagtgagat gtcttcaggg agtgagattt cccctgtgag tgaaatgcct
421 tctagtagtg aaccgtcctc gggagccgac tatgactact cagaagagta tgataacgaa
481 ccacaaatac ctggctatat tgtcgatgat tcagtcagag ttgaacaggt agttaagccc
541 ccccaaaaca agacggaaag tgaaaatact tcagataaac ccaaaagaaa gaaaaaggga
601 ggcaaaaatg gaaaaaatag aagaaacaga aagaagaaaa atccatgtaa tgcagaattt
661 caaaatttct gcattcacgg agaatgcaaa tatatagagc acctggaagc agtaacatgc
721 aaatgtcagc aagaatattt cggtgaacgg tgtggggaaa agtccatgaa aactcacagc
781 atgattgaca gtagtttatc aaaaattgca ttagcagcca tagctgcctt tatgtctgct
841 gtgatcctca cagctgttgc tgttattaca gtccagctta gaagacaata cgtcaggaaa
901 tatgaaggag aagctgagga acgaaagaaa cttcgacaag agaatggaaa tgtacatgct
961 atagcataac tgaagataaa attacaggat atcacattgg agtcactgcc aagtcatagc
1021 cataaatgat gagtcggtcc tctttccagt ggatcataag acaatggacc ctttttgtta
1081 tgatggtttt aaactttcaa ttgtcacttt ttatgctatt tctgtatata aaggtgcacg
1141 aaggtaaaaa gtatttttc aagttgtaaa taatttattt aatatttaat ggaagtgtat
1201 ttattttaca gctcattaaa ctttttaac caaacagaaa aaaaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa

Figure 24. (Page 19 of 46)

M90357 Human basic transcription factor 3

1 ttatggttaa tgttcttata gacatccaaa ggtcagaaac tattcccatt tgaaaaatat
61 ctgttgtggt ataaatgtgc tgttttcttt cctcttctcc ctgactttag ggaactgctc
121 gcagaaagaa gaaggtggtt catagaacag ccacagcaga tgacaaaaaa cttcagttct
181 ccttaaagaa gttaggggta aacaatatct ctggtattga agaggcaagt atcaaatttt
241 gttactttaa aaaacaagat ttggctggga aaagttaacg ttaatgcatt aaatgggttg
301 ttgggttttt tttaacttag ggacttcaaa gtccctaaga tgtgtttcta ccataaatta
361 ataaatatca gggagctcat taagtctgaa tgctattaga atacatattc cattccaggc
421 aaaatttcac ctgtgcttac acgtgaaata ctagttagcc agagctagtt taataaaaca
481 tttgttttta aagagactgg tcagcattgc taatttaaat ttttcttttc ttaataggtg
541 aatatgttta caaaccaagg aacagtgatc cactttaaca accctaaagt tcaggcatct
601 ctggcagcga acactttcac cattacaggc catgctgaga caaagcagct gacagaaatg
661 ctacccagca tcttaaaacca gcttggtgcg gatagtctga ctagtttaag gagactggcc
721 gaagctctgc ccaaacaatg tgagtttcct agtaatggtt ttaccaggga attactcatt
781 tagcagctga tttctgatct cagggctcag aatggatatg agtatttta agtttggaaa
841 tgcaagcttt aaaaataaca gatttgtaac tgattttaag caactgtcct tgctcaagtt
901 tgcagtaatt gatgtagcgt gccatgattg ttacacttga ttttgtggaa tgttttctac
961 ttacttgatt tggatcagat acttttatta actagaaatg atgaaaatgt taatttggtg
1021 ctttgccaat aactacttgt aagtttggaa ttgaaaaaaa aattagtgta aattatgaaa
1081 ttacttcagt ttcatctata tagttcgtat taccagtaat cttttaaaaa tggcttgcca
1141 gtattctggc attttaatta cagtgtgata gggatttatt cggggcagaa aatagtgtag
1201 ctgaatatac atctgaggat gtggcagtgt tatgctgttt tctgtgctta aaatttgaa
1261 gaataggaat gcaggaggaa gtcagaggct tatatatggc tctttagtta cccatgtttt
1321 tctaggtatt gacttaatct gcctcaattt tcatttttat tatcacattg agttgcaggt
1381 tctaaactgt cagggctttc agagctgaaa taggcttttg aagtatccca ctgatgcctg
1441 tatgggccta gtacataact ctcctgtgta cgttcatatt cttgtgtgat aaaggagagt
1501 ggatgcttac cactcacaga ctctttaatt tttttacttt aacttttttc atttcagtaa
1561 gtggttgttg agcatcaccc ttatgccaca cacagagtag ttgagaaaat ggcatcttca
1621 tttgtctccc aaaatctcac catgatttgg tatgtgggtt ttacctgcac tctaagagtt
1681 ccctactgcc cttatactac ctcaggccta tggtggccag aggattgaaa gagtggtatg
1741 gaatttgttt gttggcgttc ctagtatttt aacccatttg tagacattag aatatcatgt
1801 tattgatagt atcataggat aaaatcccaa atgtccctta tcatggaaat aagttgtaac
1861 aacacttggc atttcatctg ttctttttt ttttttttt ttttttttgg tgaatattta
1921 ttaaaaacct agacaaataa tgtttacatt ttcctttcat agctgtggat ggaaaagcac
1981 cacttgctac tggagaggat gatgatgatg aagttccagg taggaacgtt tgcttgtggt
2041 taacctagag aatcttagcc aagggagaat aagaaatctt tgtaggaaaa actacccagg
2101 gaagaggggt ggtaagttaa gatggacata gatcttactt agaatgagaa aaataatgca
2161 gtattaggta attgagaatt atgtttatag acttgacttg gcttgtttct gtttgggatc
2221 ccaaggatgt gtaggtatct aaccttaaat attgaataaa taagtatata tatatagtac
2281 cctaaatata actattacct gcagagcact aatgaccctt gctccctact ttgaaactca
2341 tgaatttaca agaaggtgtg gagttgttca ggtatcttgg gatatatata tgcattctaa
2401 aatctgtagc agcataactc cttttgggaa tcagaggatt ttgtctctta cctgttattg
2461 gataaattta cgttcttcta aaatatttat tgggcaggag aatcactgga ctcataaata
2521 ttcccacttt gcatagacag gtatccttag gaatcaggaa aattttaaca ttgtgtgtca
2581 ttgtattctt tggttctgct cccccactat tgaccaatgt agagatggga agaggggggc
2641 atttttttct cttttttttt ttttgcatt cttgttcttg gggctatgac acagtattta
2701 tcatcattgg caaatgaatg ctctttcctt catccccttt taatatctga taattatttg
2761 tagattggct tttttaagaa tttctactct ttttcttttc ctagatcttg tggagaattt

Figure 24. (Page 20 of 46)

2821 tgatgaggct tccaagaatg aggcaaactg aattgagtca acttctgaag ataaaacctg
2881 aagaagttta ctgggagctg ctattttata ttatgactgc tttttaagaa aatttttgtt
2941 tatggatctg ataaaatcta gatctctaat atttttaagc ccaagcccct tggacactgc
3001 agctcttttc agtttttgct tatacacaat tcattctttg cagctaatta agccgaagaa
3061 gcctgggaat caagtttgaa acaaagatta ataaagttct tttgcctagt atacagtttt
3121 atttttttat ttattgacac cgatctgtac acagtaaaaa aaattgctta tagaaagcta
3181 atcatggcat gtaatatggc tgataacctt tggaatttga ttaaagattt aaaatcacgg
3241 tgtaagtgta acaaaggtgg tataaagttc tcaggtttga aaactttgtc tccaacagtc
3301 cttagtgctt ccatgattta tatggtgggt gtaaatatga gaatagagta ttccttagtg
3361 gataaacaga catttctccc tgatattctc tattgtaagc atatgttaag tgccttttat
3421 gaattaccct cggtgttatc ttcctttatt cctcaatttg tgaagaacta atagctccat
3481 tttgtagatg taacctgagg tttagaactt ctaaaaagta aaagtaatct ccagatccct
3541 tctttgtagg atattttata aggtgacttg gaaaaggtag tgtttagaat aggagtggct
3601 cctgggtcat tgtcttttcc ttaagtgtaa cacctaataa atgaataggg ttatgttttt
3661 atttaataaa aaatatacag taaaattgag catatacagt taaaagaatt tataatgtct
3721 gccactataa ccaggcttac cagacagttt catggtccag aaaatcccta aacatagggt
3781 tacttttaaa cattttacaa attacaatga aacaattgtg taatctgaac caaggccatt
3841 tgaggagaaa tagttctact tgtatggtat ttatttttaa atttttcata gcaatttgca
3901 agtacctttt gaaagtatta tcagttgtat ctaaaatgca ctattaaccg tgg

Figure 24. (Page 21 of 46)

NM_006219 Homo sapiens phosphoinositide-3-kinase, p110 subunit

1 atgtgcttca gtttcataat gcctcctgct atggcagaca tccttgacat ctgggcggtg
61 gattcacaga tagcatctga tggctccata cctgtggatt tccttttgcc cactgggatt
121 tatatccagt tggaggtacc tcgggaagct accatttctt atattaagca gatgttatgg
181 aagcaagttc acaattaccc aatgttcaac ctccttatgg atattgactc ctatatgttt
241 gcatgtgtga atcagactgc tgtatatgag gagcttgaag atgaaacacg aagactctgt
301 gatgtcagac cttttcttcc agttctcaaa ttagtgacaa gaagttgtga cccaggggaa
361 aaattagact caaaaattgg agtccttata ggaaaaggtc tgcatgaatt tgattccttg
421 aaggatcctg aagtaaatga atttcgaaga aaaatgcgca aattcagcga ggaaaaaatc
481 ctgtcacttg tgggattgtc ttggatggac tggctaaaac aaacatatcc accagagcat
541 gaaccatcca tccctgaaaa cttagaagat aaactttatg ggggaaagct catcgtagct
601 gttcattttg aaaactgcca ggacgtgttt agctttcaag tgtctcctaa tatgaatcct
661 atcaaagtaa atgaattggc aatccaaaaa cgtttgacta ttcatgggaa ggaagatgaa
721 gttagcccct atgattatgt gttgcaagtc agcgggagag tagaatatgt ttttggtgat
781 catccactaa ttcagttcca gtatatccgg aactgtgtga tgaacagagc cctgccccat
841 tttatacttg tggaatgctg caagatcaag aaaatgtatg aacaagaaat gattgccata
901 gaggctgcca taaatcgaaa ttcatctaat cttcctcttc cattaccacc aaagaaaaca
961 cgaattattt ctcatgtttg ggaaaataac aacccttttcc aaattgtctt ggttaaggga
1021 aataaactta acacagagga aactgtaaaa gttcatgtca gggctggtct ttttcatggt
1081 actgagctcc tgtgtaaaac catcgtaagc tcagaggtat cagggaaaaa tgatcatatt
1141 tggaatgaac cactggaatt tgatattaat atttgtgact taccaagaat ggctcgatta
1201 tgttttgctg tttatgcagt tttggataaa gtaaaaacga agaaatcaac gaaaactatt
1261 aatccctcta aatatcagac catcaggaaa gctggaaaag tgcattatcc tgtagcgtgg
1321 gtaaatacga tggtttttga ctttaaagga caattgagaa ctggagacat aatattacac
1381 agctggtctt catttcctga tgaactcgaa gaaatgttga atccaatggg aactgttcaa
1441 acaaatccat atactgaaaa tgcaacagct ttgcatgtta aatttccaga gaataaaaaa
1501 caaccttatt attaccctcc cttcgataag attattgaaa aggcagctga gattgcaagc
1561 agtgatagtg ctaatgtgtc aagtcgaggt ggaaaaaagt ttcttcctgt attgaaagaa
1621 atcttggaca gggatccctt gtctcaactg tgtgaaaatg aaatggatct tatttggact
1681 ttgcgacaag actgccgaga gattttccca caatcactgc caaaattact gctgtcaatc
1741 aagtggaata aacttgagga tgttgctcag cttcaggcgc tgcttcagat ttggcctaaa
1801 ctgccccccc gggaggccct agagcttctg gatttcaact atccagacca gtacgttcga
1861 gaatatgctg taggctgcct gcgacagatg agtgatgaag aactttctca atatctttta
1921 caactggtgc aagtgttaaa atatgagcct tttcttgatt gtgccctctc tagattccta
1981 ttagaaagag cacttggtaa tcggaggata gggcagtttc tattttggca tcttaggtca
2041 gaagtgcaca ttcctgctgt ctcagtacaa tttggtgtca tccttgaagc atactgccgg
2101 ggaagtgtgg ggcacatgaa agtgctttct aagcaggttg aagcactcaa taagttaaaa
2161 actttaaata gtttaatcaa actgaatgcc gtgaagttaa acagagccaa agggaaggag
2221 gccatgcata cctgtttaaa acagagtgct taccgggaag ccctctctga cctgcagtca
2281 cccctgaacc catgtgttat cctctcagaa ctctatgttg aaaagtgcaa atacatggat
2341 tccaaaatga agcctttgtg gctggtatac aataacaagg tatttggtga ggattcagtt
2401 ggagtgattt ttaaaaatgg tgatgattta cgacaggata tgttgacact ccaaatgttg
2461 cgcttgatgg atttactctg gaaagaagct ggtttggatc ttcggatgtt gccttatggc
2521 tgtttagcaa caggagatcg ctctggcctc attgaagttg tgagcacctc tgaaacaatt
2581 gctgacattc agctgaacag tagcaatgtg gctgctgcag cagccttcaa caaagatgcc
2641 cttctgaact ggcttaaaga atacaactct ggggatgacc tggaccgagc cattgaggaa
2701 tttacactgt cctgtgctgg ctactgtgta gcttcttatg tccttgggat tggtgacaga

Figure 24. (Page 22 of 46)

2761 catagtgaca acatcatggt caaaaaaact ggccagctct tccacattga ctttggacat
2821 attcttggaa atttcaaatc taagtttggc attaaaaggg agcgagtgcc ttttattctt
2881 acctatgatt tcatccatgt cattcaacaa ggaaaaacag gaaatacaga aaagtttggc
2941 cggttccgcc agtgttgtga ggatgcatat ctgattttac gacggcatgg gaatctcttc
3001 atcactctct ttgcgctgat gttgactgca gggcttcctg aactcacatc agtcaaagat
3061 atacagtatc ttaaggactc tcttgcatta gggaagagtg aagaagaagc actcaaacag
3121 tttaagcaaa aatttgatga ggcgctcagg gaaagctgga ctactaaagt gaactggatg
3181 gcccacacag ttcggaaaga ctacagatct taa

Figure 24. (Page 23 of 46)

X04412 Human Gelsolin

1 gccgtgtcgc caccatggct ccgcaccgcc ccgcgcccgc gctgctttgc gcgctgtccc
61 tggcgctgtg cgcgctgtcg ctgcccgtcc gcgcggccac tgcgtcgcgg ggggcgtccc
121 aggcgggggc gccccagggg cgggtgcccg aggcgcggcc caacagcatg gtggtggaac
181 accccgagtt cctcaaggca gggaaggagc ctggcctgca gatctggcgt gtggagaagt
241 tcgatctggt gcccgtgccc accaaccttt atggagactt cttcacgggc gacgcctacg
301 tcatcctgaa gacagtgcag ctgaggaacg gaaatctgca gtatgacctc cactactggc
361 tgggcaatga gtgcagccag gatgagagcg gggcggccgc catctttacc gtgcagctgg
421 atgactacct gaacggccgg gccgtgcagc accgtgaggt ccagggcttc gagtcggcca
481 ccttcctagg ctacttcaag tctggcctga agtacaagaa aggaggtgtg gcatcaggat
541 tcaagcacgt ggtacccaac gaggtggtgg tgcagagact cttccaggtc aaagggcggc
601 gtgtggtccg tgccaccgag gtacctgtgt cctgggagag cttcaacaat ggcgactgct
661 tcatcctgga cctgggcaac aacatccacc agtggtgtgg ttccaacagc aatcggtatg
721 aaagactgaa ggccacacag gtgtccaagg gcatccggga caacgagcgg agtggccggg
781 cccgagtgca cgtgtctgag gagggcactg agcccgaggc gatgctccag gtgctgggcc
841 ccaagccggc tctgcctgca ggtaccgagg acaccgccaa ggaggatgcg gccaaccgca
901 agctggccaa gctctacaag gtctccaatg gtgcagggac catgtccgtc tccctcgtgg
961 ctgatgagaa ccccttcgcc cagggggccc tgaagtcaga ggactgcttc atcctggacc
1021 acggcaaaga tgggaaaatc tttgtctgga aaggcaagca ggcaaacacg gaggagagga
1081 aggctgccct caaaacagcc tctgacttca tcaccaagat ggactacccc aagcagactc
1141 aggtctcggt ccttcctgag ggcggtgaga ccccactgtt caagcagttc ttcaagaact
1201 ggcgggaccc agaccagaca gatggcctgg gcttgtccta cctttccagc catatcgcca
1261 acgtggagcg ggtgcccttc gacgccgcca ccctgcacac ctccactgcc atggccgccc
1321 agcacggcat ggatgacgat ggcacaggcc agaaacagat ctggagaatc gaaggttcca
1381 acaaggtgcc cgtggaccct gccacatatg gacagttcta tggaggcgac agctacatca
1441 ttctgtacaa ctaccgccat ggtggccgcc aggggcagat aatctataac tggcagggtg
1501 cccagtctac ccaggatgag gtcgctgcat ctgccatcct gactgctcag ctggatgagg
1561 agctgggagg taccccctgtc cagagccgtg tggtccaagg caaggagccc gcccacctca
1621 tgagcctgtt tggtgggaag cccatgatca tctacaaggg cggcacctcc cgcgagggcg
1681 ggcagacagc ccctgccagc acccgcctct tccaggtccg cgccaacagc gctggagcca
1741 cccgggctgt tgaggtattg cctaaggctg gtgcactgaa ctccaacgat gcctttgttc
1801 tgaaaacccc ctcagccgcc tacctgtggg tgggtacagg agccagcgag gcagagaaga
1861 cgggggccca ggagctgctc agggtgctgc gggcccaacc tgtgcaggtg gcagaaggca
1921 gcgagccaga tggcttctgg gaggccctgg gcgggaaggc tgcctaccgc acatccccac
1981 ggctgaagga caagaagatg gatgcccatc ctcctcgcct ctttgcctgc tccaacaaga
2041 ttggacgttt tgtgatcgaa gaggttcctg gtgagctcat gcaggaagac ctggcaacgg
2101 atgacgtcat gcttctggac acctgggacc aggtctttgt ctgggttgga aaggattctc
2161 aagaagaaga aaagacagaa gccttgactt ctgctaagcg gtacatcgag acggacccag
2221 ccaatcggga tcggcggacg cccatcaccg tggtgaagca aggctttgag cctccctcct
2281 ttgtgggctg gttccttggc tgggatgatg attactggtc tgtggacccc ttggacaggg
2341 ccatggctga gctggctgcc tgaggagggg cagggcccac ccatgtcacc ggtcagtgcc
2401 ttttggaact gtccttccct caaagaggcc ttagagcgag cagagcagct ctgctatgag
2461 tgtgtgtgtg tgtgtgtgtt gtttcttttt ttttttttta cagtatccaa aaatagccct
2521 gcaaaaattc agagtccttg caaaattgtc taaaatgtca gtgtttggga aattaaatcc
2581 aataaaaaca ttttgaagtg tg

Figure 24. (Page 24 of 46)

NM_001759 Homo sapiens Cyclin D2

1 agagcgagca ggggagagcg agaccagttt taaggggagg accggtgcga gtgaggcagc
61 cccgaggctc tgctcgccca ccacccaatc ctcgcctccc ttctgctcca ccttctctct
121 ctgccctcac ctctcccccg aaaaccccct atttagccaa aggaaggagg tcaggggaac
181 gctctcccct ccccttccaa aaaacaaaaa cagaaaaacc cttttccagg ccggggaaag
241 caggagggag aggggccgcc gggctggcca tggagctgct gtgccacgag gtggacccgg
301 tccgcagggc cgtgcgggac cgcaacctgc tccgagacga ccgcgtcctg cagaacctgc
361 tcaccatcga ggagcgctac cttccgcagt gctcctactt caagtgcgtg cagaaggaca
421 tccaacccta catgcgcaga atggtggcca cctggatgct ggaggtctgt gaggaacaga
481 agtgcgaaga agaggtcttc cctctggcca tgaattacct ggaccgtttc ttggctgggg
541 tcccgactcc gaagtcccat ctgcaactcc tgggtgctgt ctgcatgttc ctggcctcca
601 aactcaaaga gaccagcccg ctgaccgcgg agaagctgtg catttacacc gacaactcca
661 tcaagcctca ggagctgctg gagtgggaac tggtggtgct ggggaagttg aagtggaacc
721 tggcagctgt cactcctcat gacttcattg agcacatctt gcgcaagctg ccccagcagc
781 gggagaagct gtctctgatc cgcaagcatg ctcagacctt cattgctctg tgtgccaccg
841 actttaagtt tgccatgtac ccaccgtcga tgatcgcaac tggaagtgtg ggagcagcca
901 tctgtgggct ccagcaggat gaggaagtga gctcgctcac ttgtgatgcc ctgactgagc
961 tgctggctaa gatcaccaac acagacgtgg attgtctcaa agcttgccag gagcagattg
1021 aggcggtgct cctcaatagc ctgcagcagt accgtcagga ccaacgtgac ggatccaagt
1081 cggaggatga actggaccaa gccagcaccc ctacagacgt gcgggatatc gacctgtgag
1141 gatgccagtt gggccgaaag agagagacgc gtccataatc tggtctcttc ttctttctgg
1201 ttgtttttgt tctttgtgtt ttagggtgaa acttaaaaaa aaaattctgc ccccacctag
1261 atcatattta aagatctttt agaagtgaga gaaaaaggtc ctacgaaaac ggaataataa
1321 aaagcatttg gtgcctattt gaagtacagc ataagggaat cccttgtata tgcgaacagt
1381 tattgtttga ttatgtaaaa gtaatagtaa aatgcttaca ggaaaacctg cagagtagtt
1441 agagaatatg tatgcctgca atatgggaac aaattagagg agacttttt ttttcatgtt
1501 atgagctagc acatacaccc ccttgtagta taatttcaag gaactgtgta cgccatttat
1561 ggcatgatta gattgcaaag caatgaactc aagaaggaat tgaaataagg agggacatga
1621 tggggaagga gtacaaaaca atctctcaac atgattgaac catttgggat ggagaagcac
1681 ctttgctctc agccacctgt tactaagtca ggagtgtagt tggatctcta cattaatgtc
1741 ctcttgctgt ctacagtagc tgctacctaa aaaaagatgt tttattttgc cagttggaca
1801 caggtgattg gctcctgggt ttcatgttct gtgacatcct gcttcttctt ccaaatgcag
1861 ttcattgcag acaccaccat attgctatct aatggggaaa tgtagctatg ggccataacc
1921 aaaactcaca tgaaacggag gcagatggag accaagggtg ggatccagaa tggagtcttt
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2101 cgaaaagcac tttgaaaaat tgttcccgag cgatagatgg gatggtttat gcaagtcatg
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2221 tcttcgcttc tggtatctgg cgttctttgg tacacagttc tggtgttcct accaggactc
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2341 taaaatctgt taccattctg atggcacaga aggatcttaa ttcccatctc tatacttctc
2401 ctttggacat ggaaagaaaa gttattgctg gtgcaaagat agatggctga acatcagggt
2461 gtggcatttt gttccctttt ccgtttttt ttttttatt gttgttgtta attttattgc
2521 aaagttgtat tcagcgtact tgaatttttc ttcctctcca cttcttagag gcattcagtt
2581 agcaaagagg ttggagcaac aacttttttt ttttttttg cacaattgta attgacaggt
2641 aatgaagcta tttgttaaaa tatttgcctt tttaagtaaa aaagaaaaat cagaacaggg
2701 ctatttgaag aattatttta tacacagatt ctgccttgtt tcatagtatg agggttgaag
2761 acggaaaaca atctaagggt ctctcatttt tttaattttg ttttgttcag tttggttttt

Figure 24. (Page 25 of 46)

2821 ttttttttt gcgctgctaa gaagctaaag tcatccatcc ttattcacgt tgacagtacc
2881 tagctgtaat gtttcacaga gtgtgctgct attttataaa catttttata atatattatt
2941 ttactgctta aattccaagt cctgaagtag atggttgaga tatgagttct tcgtactgga
3001 aaagcccttc cgtagtttgt tttcttctgg tagcatattc atggttgttt ttttttttct
3061 tttttggttt tttggttttt tttttttcct ctgatcacat tcttcaaaga cggagtattc
3121 tttacctcag gtttactgga caaaatcaat aactacaaaa ggcaatgatt cacgcttttg
3181 ttttcataat acctcacaac cgtacagttt ctgcttggga gcccattcgc atgaggaata
3241 cagaagcagt gtgagcaggg ctgactccct ctcaggtgga aggcagggcg gtctcactcc
3301 cagggacctt tttggtcatg gaggccatcg ggctcccagt tagaccctgg tatcctcatc
3361 atgatggaaa aaatacattg aaccaaggga tcctccctcc ccttcaaggc agacgttcag
3421 tacaaacatt tatgcggtag gctcagatgt cgtaatttgc acttaggtac caggtgtcag
3481 gaaacagact aaaaagaatt ccaccaggct gtttggagat cctcatcttg gagctttttc
3541 aaaagcgggg cttcatctgc aaagggccct ttcatcttga agtttttccc ctccgtcttt
3601 cccctcccct ggcatggaca ccttgtgttt aggatcatct ctgcaggttt cctaggtctg
3661 aatctgcgag tagatgaacc tgcagcaagc agcgtttatg gtgcttcctt ctccctcctc
3721 tgtctcaaac tgcgcaggca agcactatgc aagcccaggc cctctgctga gcggtactaa
3781 acggtcgggt tttcaatcac actgaattgg caggataaga aaaataggtc agataagtat
3841 gggatgatag ttgaagggag gtgaagaggc tgcttctcta cagaggtgaa attccagatg
3901 agtcagtctc ttgggaagtg tgtttagaag ggttcaggac tttgtgagtt agcatgaccc
3961 taaaattcta ggggatttct ggtgggacaa tgggtggtga attttgaagt tttggagagg
4021 gaagtggagc agccagcaag taagctagcc agagttttct caagagccag ctttgctcag
4081 cacactctcc tgggccccaa ggagtcccac ggaatgggga aagtgggaac cctggagttc
4141 ttgggaatct tggagcctaa agagaaaccg aggtgcaaat tcatttcatg gtgactgacc
4201 cttgagctta aacagaagca gcaaatgaaa gaaccggaca aataaggaag ggcacaagcc
4261 tacccgactc tatttacagt ctgtaacttt ccactcttcc tgtagtcccg aggcccctgg
4321 gtccttctag cttttctctt tcccatcctt ggggccttgt gtgatgatgg gtgtggggct
4381 gccgatggga aagtcggggg ttgttaggct tttctgcctg ctcctgctta aacacaagaa
4441 ggaatcctgg attttgccct ctccttagct cttagtctct ttggtaggag ttttgttcca
4501 gaggagctct ccccccttgga tttgaacttg ctctttttgt tgttgttgtt ctttctcttc
4561 tttttcttac ctcccactaa aggggttcca aattatcctg gtctttttct accttgttgt
4621 gtttctatct cgtctttact tccatctgtt tgtttttttc tccatcagtg ggggccgagt
4681 tgttccccca gcctgccaaa ttttgatcct tcccctcttt tggccaaatc ctaggggggaa
4741 gaaatcctag tatgccaaaa atatatgcta agcataatta aactccatgc gggtccataa
4801 cagccaagaa gcctgcagga gaaagccaag ggcagttccc tccgcagaac accccatgcg
4861 tgctgagagg cgagctcctt gaagaagggg ctgttcttcc aggaggcctt attttgaact
4921 gcctcaggac cccactggag agcacagcat gccttactac tgggtcatcc ttggtctatg
4981 tgctctgtac tggaggctct gttctgcctc ttatcagcca ggtcaggggc acacatggct
5041 taagtgacaa agccagagga gaagacaacc ctgacagcat cacgctgcat cccattgcta
5101 gcaggattgg caactcttca gacggagctg cgcttccctg cagtctagca cctctagggc
5161 ctctccagac tgtgccctgg gagctctggg actgaaaggt taagaacata aggcaggatc
5221 agatgactct ctccaagagg gcaggggaat tttctctcca tgggccacag gggacagggc
5281 tgggagaaga aatagacttg caccttatgt catgtaaata attgattttc tagttcaaga
5341 agataatatt ggtagtgtgg gaattggagg taggaagggg aggaagtctg agtaagccag
5401 ttggcttcta agccaaaagg attcctcttt gtttatctct gagacagtcc aaccttgaga
5461 atagctttaa aagggaaatt aatgctgaga tgataaagtc cccttaagcc aacaaaccct
5521 ctgtagctat agaatgagtg caggtttcta ttggtgtgga ctcagagcaa tttacaagag
5581 ctgttcatgc agccatccat ttgtgcaaaa tagggtaaga agattcaaga ggatatttat
5641 tacttcctca taccacatgg cttttgatga ttctggattc taaacaaccc agaatggtca
5701 tttcaggcac aacgatacta cattcgtgtg tgtctgcttt taaacttggc tgggctatca

Figure 24. (Page 26 of 46)

5761 gaccctattc tcggctcagg ttttgagaag ccatcagcaa atgtgtacgt gcatgctgta
5821 gctgcagcct gcatcccttc gcctgcagcc tactttgggg aaataaagtg ccttactgac
5881 tgtagccatt acagtatcca atgtcttttg acaggtgcct gtccttgaaa aacaaagttt
5941 ctatttttat ttttaattgg tttagttctt aactgctggc caactcttac atccccagca
6001 aatcatcggg ccattggatt ttttccatta tgttcatcac ccttatatca tgtacctcag
6061 atctctctct ctctcctctc tctcagttat atagtttctt gtcttggact tttttttct
6121 tttctttttc ttttttttt tgctttaaaa caagtgtgat gccatatcaa gtccatgtta
6181 ttctctcaca gtgtactcta taagaggtgt gggtgtctgt ttggtcagga tgttagaaag
6241 tgctgataag tagcatgatc agtgtatgcg aaaaggtttt taggaagtat ggcaaaaatg
6301 ttgtattggc tatgatggtg acatgatata gtcagctgcc ttttaagagg tcttatctgt
6361 tcagtgttaa gtgatttaaa aaaataataa cctgttttct gactagttta aagatggatt
6421 tgaaaatggt tttgaatgca attaggttat gctatttgga caataaactc accttgacct

Figure 24. (Page 27 of 46)

NM_004444 Ephrin Receptor (EphB4)

1 cgtccacccg cccagggaga gtcagacctg ggggggcgag ggccccccaa actcagttcg
61 gatcctaccc gagtgaggcg gcgccatgga gctccgggtg ctgctctgct gggcttcgtt
121 ggccgcagct ttggaagaga ccctgctgaa cacaaaattg gaaactgctg atctgaagtg
181 ggtgacattc cctcaggtgg acgggcagtg ggaggaactg agcggcctgg atgaggaaca
241 gcacagcgtg cgcacctacg aagtgtgtga agtgcagcgt gccccgggcc aggcccactg
301 gcttcgcaca ggttgggtcc cacggcgggg cgccgtccac gtgtacgcca cgctgcgctt
361 caccatgctc gagtgcctgt ccctgcctcg ggctgggcgc tcctgcaagg agaccttcac
421 cgtcttctac tatgagagcg atgcggacac ggccacggcc ctcacgccag cctggatgga
481 gaacccctac atcaaggtgg acacggtggc cgcggagcat ctcacccgga agcgccctgg
541 ggccgaggcc accgggaagg tgaatgtcaa gacgctgcgt ctgggaccgc tcagcaaggc
601 tggcttctac ctggccttcc aggaccaggg tgcctgcatg gccctgctat ccctgcacct
661 cttctacaaa aagtgcgccc agctgactgt gaacctgact cgattcccgg agactgtgcc
721 tcgggagctg gttgtgcccg tggccggtag ctgcgtggtg gatgccgtcc ccgcccctgg
781 ccccagcccc agcctctact gccgtgagga tggccagtgg gccgaacagc cggtcacggg
841 ctgcagctgt gctccggggt tcgaggcagc tgaggggaac accaagtgcc gagcctgtgc
901 ccagggcacc ttcaagcccc tgtcaggaga agggtcctgc cagccatgcc cagccaatag
961 ccactctaac accattggat cagccgtctg ccagtgccgc gtcgggtact tccgggcacg
1021 cacagacccc cggggtgcac cctgcaccac ccctccttcg gctccgcgga gcgtggtttc
1081 ccgcctgaac ggctcctccc tgcacctgga atggagtgcc cccctggagt ctggtggccg
1141 agaggacctc acctacgccc tccgctgccg ggagtgccga cccggaggct cctgtgcgcc
1201 ctgcgggggа gacctgactt ttgaccccgg cccccgggac ctggtggagc cctgggtggt
1261 ggttcgaggg ctacgtccgg acttcaccta taccttgag gtcactgcat tgaacggggt
1321 atcctcctta gccacggggc ccgtcccatt tgagcctgtc aatgtcacca ctgaccgaga
1381 ggtacctcct gcagtgtctg acatccgggt gacgcggtcc tcacccagca gcttgagcct
1441 ggcctgggct gttccccggg cacccagtgg ggcgtggctg gactacgagg tcaaatacca
1501 tgagaagggc gccgagggtc ccagcagcgt gcggttcctg aagacgtcag aaaaccgggc
1561 agagctgcgg gggctgaagc ggggagccag ctacctggtg caggtacggg cgcgctctga
1621 ggccggctac gggcccttcg gccaggaaca tcacagccag acccaactgg atgagagcga
1681 gggctggcgg gagcagctgg ccctgattgc gggcacggca gtcgtgggtg tggtcctggt
1741 cctggtggtc attgtggtcg cagttctctg cctcaggaag cagagcaatg ggagagaagc
1801 agaatattcg gacaaacacg gacagtatct catcggacat ggtactaagg tctacatcga
1861 ccccttcact tatgaagacc ctaatgaggc tgtgagggaa tttgcaaaag agatcgatgt
1921 ctcctacgtc aagattgaag aggtgattgg tgcaggtgag tttggcgagg tgtgccgggg
1981 gcggctcaag gccccaggga agaaggagag ctgtgtggca atcaagaccc tgaagggtgg
2041 ctacacggag cggcagcggc gtgagtttct gagcgaggcc tccatcatgg gccagttcga
2101 gcaccccaat atcatccgcc tggagggcgt ggtcaccaac agcatgcccg tcatgattct
2161 cacagagttc atggagaacg gcgccctgga ctccttcctg cggctaaacg acggacagtt
2221 cacagtcatc cagctcgtgg gcatgctgcg gggcatcgcc tcgggcatgc ggtaccttgc
2281 cgagatgagc tacgtccacc gagacctggc tgctcgcaac atcctagtca acagcaacct
2341 cgtctgcaaa gtgtctgact ttggcctttc ccgattcctg gaggagaact cttccgatcc
2401 cacctacacg agctccctgg gaggaaagat tcccatccga tggactgccc cggaggccat
2461 tgccttccgg aagttcactt ccgccagtga tgcctggagt tacgggattg tgatgtggga
2521 ggtgatgtca tttggggaga ggccgtactg ggacatgagc aatcaggacg tgatcaatgc
2581 cattgaacag gactaccggc tgcccccgcc cccagactgt cccacctccc tccaccagct
2641 catgctggac tgttggcaga aagaccggaa tgcccggccc cgcttccccc aggtggtcag
2701 cgccctggac aagatgatcc ggaaccccgc cagcctcaaa atcgtggccc gggagaatgg
2761 cggggcctca caccctctcc tggaccagcg gcagcctcac tactcagctt ttggctctgt

Figure 24. (Page 28 of 46)

2821 gggcgagtgg cttcgggcca tcaaaatggg aagatacgaa gaaagtttcg cagccgctgg
2881 ctttggctcc ttcgagctgg tcagccagat ctctgctgag gacctgctcc gaatcggagt
2941 cactctggcg ggacaccaga agaaaatctt ggccagtgtc cagcacatga agtcccaggc
3001 caagccggga accccgggtg ggacaggagg accggccccg cagtactgac ctgcaggaac
3061 tccccacccc agggacaccg cctccccatt ttccggggca gagtggggac tcacagaggc
3121 ccccagccct gtgccccgct ggattgcact ttgagcccgt ggggtgagga gttggcaatt
3181 tggagagaca ggatttgggg gttctgccat aataggaggg gaaaatcacc ccccagccac
3241 ctcggggaac tccagaccaa gggtgagggc gcctttccct caggactggg tgtgaccaga
3301 ggaaaaggaa gtgcccaaca tctcccagcc tccccaggtg ccccccctcac cttgatgggt
3361 gcgttcccgc agaccaaaga gagtgtgact cccttgccag ctccagagtg ggggggctgt
3421 cccagggggc aagaaggggt gtcagggccc agtgacaaaa tcattggggt ttgtagtccc
3481 aacttgctgc tgtcaccacc aaactcaatc attttttcc cttgtaaatg cccctccccc
3541 agctgctgcc ttcatattga aggtttttga gttttgtttt tggtcttaat ttttctcccc
3601 gttccctttt tgtttcttcg ttttgttttt ctaccgtcct tgtcataact ttgtgttgga
3661 gggaacctgt ttcactatgg cctcctttgc ccaagttgaa acaggggccc atcatcatgt
3721 ctgtttccag aacagtgcct tggtcatccc acatccccgg accccgcctg ggacccccaa
3781 gctgtgtcct atgaaggggt gtggggtgag gtagtgaaaa gggcggtagt tggtggtgga
3841 acccagaaac ggacgccggt gcttggaggg gttcttaaat tatatttaaa aaagtaactt
3901 tttgtataaa taaaagaaaa tgggacgtgt cccagctcca ggggt

Figure 24. (Page 29 of 46)

M18737 Human Hanukah Factor /granzyme A

1 atgaggaact cctatagatt tctggcatcc tctctctcag ttgtcgtttc tctcctgcta
61 attcctgaag atgtctgtga aaaaattatt ggaggaaatg aagtaactcc tcattcaaga
121 ccctacatgg tcctacttag tcttgacaga aaaaccatct gtgctggggc tttgattgca
181 aaagactggg tgttgactgc agctcactgt aacttgaaca aaaggtccca ggtcattctt
241 ggggctcact caataaccag ggaagagcca acaaaacaga taatgcttgt taagaaagag
301 tttccctatc catgctatga cccagccaca cgcgaaggtg accttaaact tttacagctg
361 acggaaaaag caaaaattaa caaatatgtg actatccttc atctacctaa aaaggggat
421 gatgtgaaac caggaaccat gtgccaagtt gcagggtggg ggaggactca caatagtgca
481 tcttggtccg atactctgag agaagtcaat atcaccatca tagacagaaa agtctgcaat
541 gatcgaaatc actataattt taaccctgtg attggaatga atatggtttg tgctggaagc
601 ctccgaggtg gaagagactc gtgcaatgga gattctggaa gccctttgtt gtgcgagggt
661 gtttttccgag gggtcacttc ctttggcctt gaaaataaat gcggagaccc tcgtgggcct
721 ggtgtctata ttcttctctc aaagaaacac ctcaactgga taattatgac tatcaaggga
781 gcagtttaaa taaccgtttc ctttcattta ctgtggcttc ttaatctttt caca

Figure 24. (Page 30 of 46)

NM_000551 von Hippel-Lindau tumor suppressor (VHL)

1 acgcagctcc gccccgcgtc cgacccgcgg atcccgcggc gtccggcccg ggtggtctgg
61 atcgcggagg gaatgccccg gagggcggag aactgggacg aggccgaggt aggcgcggag
121 gaggcaggcg tcgaagagta cggccctgaa gaagacggcg gggaggagtc gggcgccgag
181 gagtccggcc cggaagagtc cggcccggag gaactgggcg ccgaggagga gatggaggcc
241 gggcggccgc ggcccgtgct gcgctcggtg aactcgcgcg agccctccca ggtcatcttc
301 tgcaatcgca gtccgcgcgt cgtgctgccc gtatggctca acttcgacgg cgagccgcag
361 ccctacccaa cgctgccgcc tggcacgggc cgccgcatcc acagctaccg aggtcacctt
421 tggctcttca gagatgcagg gacacacgat gggcttctgg ttaaccaaac tgaattattt
481 gtgccatctc tcaatgttga cggacagcct atttttgcca atatcacact gccagtgtat
541 actctgaaag agcgatgcct ccaggttgtc cggagcctag tcaagcctga gaattacagg
601 agactggaca tcgtcaggtc gctctacgaa gatctggaag accacccaaa tgtgcagaaa
661 gacctggagc ggctgacaca ggagcgcatt gcacatcaac ggatgggaga ttgaagattt
721 ctgttgaaac ttacactgtt tcatctcagc ttttgatggt actgatgagt cttgatctag
781 atacaggact ggttccttcc ttagtttcaa agtgtctcat tctcagagta aaataggcac
841 cattgcttaa aagaaagtta actgacttca ctaggcattg tgatgtttag gggcaaacat
901 cacaaaatgt aatttaatgc ctgcccatta gagaagtatt tatcaggaga aggtggtggc
961 atttttgctt cctagtaagt caggacagct tgtatgtaag gaggtttata taagtaattc
1021 agtgggaatt gcagcatatc gtttaatttt aagaaggcat tggcatctgc ttttaatgga
1081 tgtataatac atccattcta catccgtagc ggttggtgac ttgtctgcct cctgctttgg
1141 gaagactgag gcatccgtga ggcagggaca agtctttctc ctctttgaga ccccagtgcc
1201 tgcacatcat gagccttcag tcagggtttg tcagaggaac aaaccagggg acactttgtt
1261 agaaagtgct tagaggttct gcctctattt ttgttggggg gtgggagagg ggaccttaaa
1321 atgtgtacag tgaacaaatg tcttaaaggg aatcattttt gtaggaagca ttttttataa
1381 ttttctaagt cgtgcacttt ctcggtccac tcttgttgaa gtgctgtttt attactgttt
1441 ctaaactagg attgacattc tacagttgtg ataatagcat ttttgtaact tgccatccgc
1501 acagaaaata cgagaaaatc tgcatgtttg attatagtat taatggacaa ataagttttt
1561 gctaaatgtg agtatttctg ttccttttg taaatatgtg acattcctga ttgatttggg
1621 tttttttgtt gttgttgttt tgttttgttt tgtttttttg ggatggagkc tcactcttgt
1681 cacccaggct ggagtgcagt ggcgccatct cggctcactg caacctctgc ctcctgagtt
1741 cacgtaatcc tcctgagtag ctgggattac aggtgcctgc caccacgctg gccaattttt
1801 gtacttttag tagagacagt gtttcgccat gttggccagg ctggtttcaa actcctgacc
1861 tcaggtgatc cgcccacctc agcctcccaa aatggtggga ttacaggtgt gtgggccacc
1921 gtgcctggct gattcagcat tttttatcag gcaggaccag gtggacttcc acctccagcc
1981 tctggtccta ccaatggatt catggagtag cctggactgt ttcatagttt tctaaatgta
2041 caaattctta taggctagac ttagattcat taactcaaat tcaatgcttc tatcagactc
2101 agtttttgt aactaataga ttttttttc cacttttgtt ctactccttc cctaatagct
2161 ttttaaaaaa atctccccag tagagaaaca tttggaaaag acagaaaact aaaaaggaag
2221 aaaaaagatc cctattagat acacttctta aatacaatca cattaacatt ttgagctatt
2281 tccttccagc ctttttaggg cagattttgg ttggttttta catagttgag attgtactgt
2341 tcatacagtt ttataccctt tttcatttaa ctttataact taaatattgc tctatgttag
2401 tataagcttt tcacaaacat tagtatagtc tccctttat aattaatgtt tgtgggtatt
2461 tcttggcatg catctttaat tccttatcct agcctttggg cacaattcct gtgctcaaaa
2521 atgagagtga cggctggcat ggtggctccc gcctgtaatc ccagtacttt gggaagccaa
2581 ggtaagagga ttgcttgagc ccagaacttc aagatgagcc tgggctcata gtgagaaccc
2641 gtctatacaa aaaatttta aaaattagca tggcggcaca catctgtaat cctagctact
2701 tggcaggctg aggtgagaag atcattggag tttaggaatt ggaggcggca gtgagtcatg

Figure 24. (Page 31 of 46)

2761 agtatgccgc tgcactccag cctgggggac agagcaagac cctgcctcaa aaaaaaaaaa
2821 aaaaaaaatt caggccggga atggtggttc acgcctgtaa tcccagcact ttggggggtc
2881 gaggtgggca gatcacctga ggtcaggagt tcgagaccag cctggccaac atggtaaaac
2941 cccatttcta ctaaaaaata caagaattag ctgggtgtgg tggcgcatgc ctgtaatcct
3001 agctactcag gaggctgagg caggagaatc acttgacccc aggaggcgaa gattgcagtg
3061 agctgatatc gcaccattgt actccagcct gtgtgacaga gcaatactct tgtcccaaaa
3121 aaaaaaaaaa ttcaaatcag agtgaagtga atgagacact ccagttttcc ttctactccg
3181 aattttagct cctcctttca acattcaaca aatagtcttt ttttttttt ttttttttg
3241 gggatggagt ctccctctgt tgcccaggct ggagtgcaga ggtgcgatct ctgctcacta
3301 caagctctgc ctcccgagtt caagtgattc tcctggctca ccctcctgag ctgggattac
3361 aggcgcctgc caccatgcct ggctaatttt gtgtttttag tggagacggg gtttcaccat
3421 gttgtccagg atggtcttga tctcctgacc ttgtgatcca cccacctcag cctcccaaag
3481 tggtgggatt acaggtgtga gccaccgcgt ccagccagct ttattatttt ttttaagctg
3541 tctttgtgtc aaaatgatag ttcatgctcc tcttgttaaa acctgcaggc cgagcacagt
3601 ggctcatgcc tgtaatccca gcattttggg agaccaaggc ggatggatca cctgaggtca
3661 ggagctcaag accagcctgg ctaacatggt gaaacctcat ctccacttaa aatacaaaaa
3721 ttgccggccg cggcggctca tgcctgtaat cccagcactt tgggaggcct aggcgggtgg
3781 atcacgacgt caggaaatcg agaccatcct ggctaacacg ggtgaaaccc cgtctctatt
3841 aaaaaataga aaaaattagg cgggcgtggt ggtgagcgcc tgtagtccca gctactcgag
3901 agcctgaggc aggagaatgg catgaacctg gaaggtggag cttgcagtga gctgagatgg
3961 tgccactgca ctctaacctg ggcgacagag tgagactccg tctcaaaaaa aaaaacaaaa
4021 accaaaactt atccaggtgt ggcggtgggc gcctgtgagg caggcgaatc tcttgaaccc
4081 gggaggcgga ggttgcagtg agccaagatc acaccattgc actccagcct gggaaacaag
4141 agtgaaattc catctcaaaa ccaaattttc aaaaaaaaaa catgccgctt gagtactgtg
4201 tttttggtgt tgtccaagga aaattaaaac ctgtagcatg aataatgttt gttttcattt
4261 cgaatcttgt gaatgtatta aatatatcgc tcttaagaga cggtgaagtt cctatttcaa
4321 gttttttttg ttttgttttg tttttaagct gttttttaat acattaaatg gtgctgagta
4381 aaggaaatag gcagggtgtg ttgtgtggtg ttttaactag gcgcttctct ctcagagagt
4441 tttgaaacct gtttacataa aggcccaaga tgggaaggag atccaaacat aagccaccag
4501 cctcattcca agtctcttct ctttccaacc ctggattttt ttttttatt taacattgtt
4561 tcttttagct ttatttttct tataaaagaa atgtatcact ataaaaaatt acacactaca
4621 gaaaaatatt aagaagaaaa acattcacat cggaaacaaa gttttttccc atgaaaacag
4681 aacccaaaag ggtaagtggt tagtatttca ccagcaatta tgttgagaat aaggccaggc
4741 gaggtggctc acgcctgtaa tctcagcact ttgggaggcc agggcaggca gatcatctga
4801 ggtcaggagt ttgagaccag cctggccaac atggtgaaac cctatctcta ctaaaaatta
4861 aa

Figure 24. (Page 32 of 46)

D21254 Human mRNA for OB-Cadherin-1

1 cgcggagaga tgccgcgggg gccgctcgca gccgccgctg acttgtgaat gggaccggga
61 ctggggccgg gactgacacc gcagcgcttg ccctgcgcca gggactggcg gctcggaggt
121 tgcgtccacc ctcaagggcc ccagaaatca ctgtgttttc agctcagcgg ccctgtgaca
181 ttccttcgtg ttgtcatttg ttgagtgacc aatcagatgg gtggagtgtg ttacagaaat
241 tggcagcaag tatccaatgg gtgaagaaga agctaactgg ggacgtgggc agccctgacg
301 tgatgagctc aaccagcaga gacattccat cccaagagag gtctgcgtga cgcgtccggg
361 aggccaccct cagcaagacc accgtacagt tggtggaagg ggtgacagct gcattctcct
421 gtgcctacca cgtaaccaaa aatgaaggag aactactgtt tacaagccgc cctggtgtgc
481 ctgggcatgc tgtgccacag ccatgccttt gccccagagc ggcgggggca cctgcggccc
541 tccttccatg ggcaccatga gaagggcaag gaggggcagg tgctacagcg ctccaagcgt
601 ggctgggtct ggaaccagtt cttcgtgata gaggagtaca ccgggcctga ccccgtgctt
661 gtgggcaggc ttcattcaga tattgactct ggtgatggga acattaaata cattctctca
721 ggggaaggag ctggaaccat ttttgtgatt gatgacaaat cagggaacat tcatgccacc
781 aagacgttgg atcgagaaga gagagcccag tacacgttga tggctcaggc ggtggacagg
841 gacaccaatc ggccactgga gccaccgtcg gaattcattg tcaaggtcca ggacattaat
901 gacaaccctc cggagttcct gcacgagacc tatcatgcca acgtgcctga gaggtccaat
961 gtgggaacgt cagtaatcca ggtgacagct tcagatgcag atgaccccac ttatggaaat
1021 agcgccaagt tagtgtacag tatcctcgaa ggacaaccct atttttcggt ggaagcacag
1081 acaggtatca tcagaacagc cctacccaac atggacaggg aggccaagga ggagtaccac
1141 gtggtgatcc aggccaagga catgggtgga catatgggcg gactctcagg gacaaccaaa
1201 gtgacgatca cactgaccga tgtcaatgac aacccaccaa agtttccgca gagcgtatac
1261 cagatatctg tgtcagaagc agccgtccct ggggaggaag taggaagagt gaaagctaaa
1321 gatccagaca ttggagaaaa tggcttagtc acatacaata ttgttgatgg agatggtatg
1381 gaatcgtttg aaatcacaac ggactatgaa acacaggagg gggtgataaa gctgaaaaag
1441 cctgtagatt ttgaaaccaa aagagcctat agcttgaagg tagaggcagc caacgtgcac
1501 atcgacccga agtttatcag caatggccct ttcaaggaca ctgtgaccgt caagatcgca
1561 gtagaagatg ctgatgagcc ccctatgttc ttggccccaa gttacatcca cgaagtccaa
1621 gaaaatgcag ctgctggcac cgtggttggg agagtgcatg ccaaagaccc tgatgctgcc
1681 aacagcccga taaggtattc catcgatcgt cacactgacc tcgacagatt tttcactatt
1741 aatccagagg atggttttat taaaactaca aaacctctgg atagagagga aacagcctgg
1801 ctcaacatca ctgtctttgc agcagaaatc cacaatcggc atcaggaagc caaagtccca
1861 gtggccatta gggtccttga tgtcaacgat aatgctccca agtttgctgc cccttatgaa
1921 ggtttcatct gtgagagtga tcagaccaag ccactttcca accagccaat tgttacaatt
1981 agtgcagatg acaaggatga cacggccaat ggaccaagat ttatcttcag cctacccccc
2041 gaaatcattc acaatccaaa tttcacagtc agagacaacc gagataacac agcaggcgtg
2101 tacgcccggc gtggagggtt cagtcggcag aagcaggact tgtaccttct gcccatagtg
2161 atcagcgatg gcggcatccc gcccatgagt agcaccaaca ccctcaccat caaagtctgc
2221 gggtgcgacg tgaacggggc actgctctcc tgcaacgcag aggcctacat tctgaacgcc
2281 ggcctgagca caggcgccct gatcgccatc ctcgcctgca tcgtcattct cctggtcatt
2341 gtagtattgt ttgtgaccct gagaaggcaa aagaaagaac cactcattgt ctttgaggaa
2401 gaagatgtcc gtgagaacat cattacttat gatgatgaag ggggtgggga agaagacaca
2461 gaagcctttg atattgccac cctccagaat cctgatggta tcaatggatt tatcccccgc
2521 aaagacatca aacctgagta tcagtacatg cctagacctg ggctccggcc agcgcccaac
2581 agcgtggatg tcgatgactt catcaacacg agaatacagg aggcagacaa tgaccccacg
2641 gctcctcctt atgactccat tcaaatctac ggttatgaag gcaggggctc agtggccggg
2701 tccctgagct ccctagagtc ggccaccaca gattcagact tggactatga ttatctacag
2761 aactggggac ctcgttttaa gaaactagca gatttgtatg gttccaaaga cacttttgat

Figure 24. (Page 33 of 46)

2821 gacgattctt aacaataacg atacaaattt ggccttaaga actgtgtctg gcgttctcaa
2881 gaatctagaa gatgtgtaaa caggtatttt tttaaatcaa ggaaaggctc atttaaaaca
2941 ggcaaagttt tacagagagg atacatttaa taaaactgcg aggacatcaa agtggtaaat
3001 actgtgaaat acctttttctc acaaaaaggc aaatattgaa gttgtttatc aacttcgcta
3061 gaaaaaaaaa acacttggca tacaaaatat ttaagtgaag gagaagtcta acgctgaact
3121 gacaatgaag ggaaattgtt tatgtgttat gaacatccaa gtctttcttc ttttttaagt
3181 tgtcaaagaa gcttccacaa aattagaaag gacaacagtt ctgagctgta atttcgcctt
3241 aaactctgga cactctatat gtagtgcatt tttaaacttg aaatatataa tattcagcca
3301 gcttaaaccc atacaatgta tgtacaatac aatgtacaat tatgtctctt gagcatcaat
3361 cttgttactg ctgattcttg taaatctttt tgcttctact ttcatcttaa actaatacgt
3421 gccagatata actgtcttgt ttcagtgaga gacgccctat ttctatgtca tttttaatgt
3481 atctatttgt acaattttaa agttcttatt ttagtataca tataaatatc agtattctga
3541 catgtaagaa aatgttacgg catcacactt atattttatg aacattgtac tgttgcttta
3601 atatgagctt caatataaga agcaatcttt gaaataaaaa aagatttttt tttaaaaaaa
3661 a

Figure 24. (Page 34 of 46)

D21255 Human mRNA for OB-cadherin-2

1 acaggcccgc gacgctcccc tcagctggcg gcggccgcgg agagatgccg cgggggccgc
61 tcgcagccgc cgctgacttg tgaatgggac cgggactggg gccgggactg acaccgcagc
121 gcttgccctg cgccagggac tggcggctcg gaggttgcgt ccaccctcaa gggccccaga
181 aatcactgtg ttttcagctc agcggccctg tgacattcct tcgtgttgtc atttgttgag
241 tgaccaatca gatgggtgga gtgtgttaca gaaattggca gcaagtatcc aatgggtgaa
301 gaagaagcta actggggacg tgggcagccc tgacgtgatg agctcaacca gcagagacat
361 tccatcccaa gagaggtctg cgtgacgcgt ccgggaggcc accctcagca agaccaccgt
421 acagttggtg gaaggggtga cagctgcatt ctcctgtgcc taccacgtaa ccaaaaatga
481 aggagaacta ctgtttacaa gccgccctgg tgtgcctggg catgctgtgc cacagccatg
541 cctttgcccc agagcggcgg gggcacctgc ggccctcctt ccatgggcac catgagaagg
601 gcaaggaggg gcaggtgcta cagcgctcca agcgtggctg ggtctggaac cagttcttcg
661 tgatagagga gtacaccggg cctgaccccg tgcttgtggg caggcttcat tcagatattg
721 actctggtga tgggaacatt aaatacattc tctcagggga aggagctgga accatttttg
781 tgattgatga caaatcaggg aacattcatg ccaccaagac gttggatcga gaagagagag
841 cccagtacac gttgatggct caggcggtgg acagggacac caatcggcca ctggagccac
901 cgtcggaatt cattgtcaag gtccaggaca ttaatgacaa ccctccggag ttcctgcacg
961 agacctatca tgccaacgtg cctgagaggt ccaatgtggg aacgtcagta atccaggtga
1021 cagcttcaga tgcagatgac cccacttatg gaaatagcgc caagttagtg tacagtatcc
1081 tcgaaggaca accctatttt tcggtggaag cacagacagg tatcatcaga acagccctac
1141 ccaacatgga cagggaggcc aaggaggagt accacgtggt gatccaggcc aaggacatgg
1201 gtggacatat gggcggactc tcagggacaa ccaaagtgac gatcacactg accgatgtca
1261 atgacaaccc accaaagttt ccgcagagcg tataccagat atctgtgtca gaagcagccg
1321 tccctgggga ggaagtagga agagtgaaag ctaaagatcc agacattgga gaaaatggct
1381 tagtcacata caatattgtt gatggagatg gtatggaatc gtttgaaatc acaacggact
1441 atgaaacaca ggaggggggtg ataaagctga aaaagcctgt agattttgaa accaaaagag
1501 cctatagctt gaaggtagag gcagccaacg tgcacatcga cccgaagttt atcagcaatg
1561 gccctttcaa ggacactgtg accgtcaaga tcgcagtaga agatgctgat gagccccccta
1621 tgttcttggc cccaagttac atccacgaag tccaagaaaa tgcagctgct ggcaccgtgg
1681 ttgggagagt gcatgccaaa gaccctgatg ctgccaacag cccgataagg tattccatcg
1741 atcgtcacac tgacctcgac agatttttca ctattaatcc agaggatggt tttattaaaa
1801 ctacaaaacc tctggataga gaggaaacag cctggctcaa catcactgtc tttgcagcag
1861 aaatccacaa tcggcatcag gaagccaaag tcccagtggc cattagggtc cttgatgtca
1921 acgataatgc tcccaagttt gctgcccctt atgaaggttt catctgtgag agtgatcaga
1981 ccaagccact ttccaaccag ccaattgtta caattagtgc agatgacaag gatgacacgg
2041 ccaatggacc aagatttatc ttcagcctac cccctgaaat cattcacaat ccaaatttca
2101 cagtcagaga caaccgagat aacacagcag gcgtgtacgc ccggcgtgga gggttcagtc
2161 ggcagaagca ggacttgtac cttctgccca tagtgatcag cgatggcggc atcccgccca
2221 tgagtagcac caacaccctc accatcaaag tctgcgggtg cgacgtgaac ggggcactgc
2281 tctcctgcaa cgcagaggcc tacattctga acgccggcct gagcacaggc gccctgatcg
2341 ccatcctcgc ctgcatcgtc attctcctgg gttgcccaag cttaatggaa ccccctctc
2401 ccagggaaga catgagattg ctttatctgg gcttccagct gatgctattt tcctatgtta
2461 aagtaaacag aagattttgt cttctgggggg tctttataaa acttcctttc ctctatgtgg
2521 tggctacaga gagtccaacc acacttacgt cattgtagta ttgtttgtga ccctgagaag
2581 gcaaaagaaa gaaccactca ttgtctttga ggaagaagat gtccgtgaga acatcattac
2641 ttatgatgat gaaggggtg gggaagaaga cacagaagcc tttgatattg ccaccctcca
2701 gaatcctgat ggtatcaatg gatttatccc ccgcaaagac atcaaacctg agtatcagta
2761 catgcctaga cctgggctcc ggccagcgcc caacagcgtg gatgtcgatg acttcatcaa

Figure 24. (Page 35 of 46)

2821 cacgagaata caggaggcag acaatgaccc cacggctcct ccttatgact ccattcaaat
2881 ctacggttat gaaggcaggg gctcagtggc cgggtccctg agctccctag agtcggccac
2941 cacagattca gacttggact atgattatct acagaactgg ggacctcgtt ttaagaaact
3001 agcagatttg tatggttcca aagacacttt tgatgacgat tcttaacaat aacgatacaa
3061 atttggcctt aagaactgtg tctggcgttc tcaagaatct agaagatgtg taaacaggta
3121 ttttttaaa tcaaggaaag gctcatttaa aacaggcaaa gttttacaga gaggatacat
3181 ttaataaaac tgcgaggaca tcaaagtggt aaatactgtg aaataccttt tctcacaaaa
3241 aggcaaatat tgaagttgtt tatcaacttc gctagaaaaa aaaaacactt ggcatacaaa
3301 atatttaagt gaaggagaag tctaacgctg aactgacaat gaagggaaat tgtttatgtg
3361 ttatgaacat ccaagtcttt cttctttttt aagttgtcaa agaagcttcc acaaaattag
3421 aaaggacaac agttctgagc tgtaatttcg ccttaaactc tggacactct atatgtagtg
3481 catttttaaa cttgaaatat ataatattca gccagcttaa acccatacaa tgtatgtaca
3541 atacaatgta caattatgtc tcttgagcat caatcttgtt actgctgatt cttgtaaatc
3601 tttttgcttc tactttcatc ttaaactaat acgtgccaga tataactgtc ttgtttcagt
3661 gagagacgcc ctatttctat gtcattttta atgtatctat ttgtacaatt ttaaagttct
3721 tattttagta tacatataaa tatcagtatt ctgacatgta agaaaatgtt acggcatcac
3781 acttatattt tatgaacatt gtactgttgc tttaatatga gcttcaatat aagaagcaat
3841 ctttgaaata aaaaaagatt tttttt

Figure 24. (Page 36 of 46)

NM_014935 Homo sapiens phosphoinositol 3-phosphate-binding protein-3 (PEPP)

1 gctggatcct gcagtaacca caacagcatc ctctccctgc gccagggacc tgccagccgg
61 agagatgact gattagatca gattagatcc ggagccccgc tctgcagaag ggggccccag
121 gggcgggggа ggaggacccc agctggcctg agctgggggg aggggtgcct tggggctcgc
181 agagttagag ctttccagcg cggggatcac acctcagaag ccgccacaat gaaagacgga
241 acacatttct acacccagtg actggccagg tcccagagga aaacaaaaaa tttgacttga
301 aaatatcgac cttggacatg tccaataaaa caggtgggaa acgcccggct accaccaaca
361 gtgacatacc caaccacaac atggtgtccg aggtccctcc agagcggccc agcgtccggg
421 caactcgcac agcccgcaaa gccatcgcct ttggcaagcg ctcacactcc atgaagcgga
481 accccaatgc acctgtcacc aaggcgggct ggctcttcaa acaggccagc tccggggtta
541 agcagtggaa caagcgctgg ttcgtcctgg tggatcgctg cctcttctac tataaagatg
601 agaaggaaga gagtatcctg ggcagcatcc ccctcctgag cttccgggta gccgcagtgc
661 agccctcaga caacatcagc cggaaacaca cgtttaaggc tgagcatgcc ggggtccgca
721 cctacttctt cagtgccgag agccccgagg agcaagaggc ctggatccag gccatggggg
781 aggctgctcg agtacagatc cctccagccc agaagtcagt gccccaagct gtgcggcaca
841 gccatgagaa gccagactcg gagaacgtcc cacccagcaa gcaccaccag cagccacccc
901 acaacagcct ccctaagcct gagccagagg ccaagactcg aggggagggt gatggccgag
961 gctgtgagaa ggcagagaga aggcctgaga ggccagaagt caagaaagag cctccggtga
1021 aagccaatgg cctcccagct ggaccggagc cagcctcaga gccgggcagc ccttaccccg
1081 agggcccaag agtgccaggg ggtggggaac agcctgccca gcccaatggc tggcagtacc
1141 actccccaag ccggccaggg agcacagctt tcccgtctca ggatggagag actgggggac
1201 accggcggag tttcccacca cgcaccaacc ctgacaaaat tgcccagcgc aagagctcca
1261 tgaaccagct tcagcagtgg gtgaatctgc gccgggggggt acccccgcct gaagaccttc
1321 ggagtccctc taggttctat cctgtgtctc gcagggtccc tgagtactat ggcccctact
1381 cctcccagta ccccgatgat tatcagtact acccgccagg agtgcggccg gagagcatct
1441 gttccatgcc ggcctatgat cggatcagcc cgccctgggc cctggaggac aagcgccatg
1501 ccttccgcaa tgggggtggc cctgcctacc agctgcgaga gtggaaggag cccgccagct
1561 acgggcggca ggatgccacc gtctggatcc caagcccctc ccggcagcca gtctattatg
1621 atgagctgga tgccgcctct agctccctgc gccgcctgtc cctgcagccc cgctcccact
1681 ctgtgccccg ctcacccagc cagggctcct acagccgtgc ccgcatttac tcccctgtcc
1741 gctcacccag tgcccgtttt gagcggctgc cacctcgcag tgaggacatc tatgctgacc
1801 ctgctgccta tgtgatgagg cgatccatca gctcccccaa ggtccctcca tacccagaag
1861 tgttccggga cagcctccac acctacaagt taaacgagca agacacagat aagctgctgg
1921 gaaaattgtg tgagcagaac aaggtggtga gggagcagga ccggctggtg cagcagctcc
1981 gagctgagaa ggagagcctg gaaagtgcct tgatggggac ccaccaggag ctggagatgt
2041 ttggaagcca gcccgcctac ccagaaaagc tgcgacacaa aaaggattca ctgcagaacc
2101 agctcatcaa catccgcgtg gagctgtctc aggcgaccac ggccctgaca aacagcacca
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2221 tcaatttgga cacccagaat gaggtgctga accggcaaat ccaaaaggag atctggagga
2281 tccaggacgt gatggagggg ctgaggaaga acaacccctc ccggggcacg gacaccgcca
2341 agcacagagg aggacttggc ccctcagcca cctacagctc caacagcccg gccagccccc
2401 tcagctctgc cagcctcacc agccccctga gccccttttc actggtgtcg ggctctcagg
2461 ggtcccccac caagcctggc tccaacgagc ccaaggcaaa ctatgaacaa agcaagaaag
2521 acccccacca gacattgccc ctggacaccc ccagagacat cagccttgtg cccaccaggc
2581 aagaggtaga ggcagagaag caggcagctc tcaacaaagt tggcgttgtg ccccctcgga
2641 caaaatcgcc cactgatgat gaggtgaccc catcagcagt ggtaagaagg aatgccagtg
2701 ggctcaccaa tggactctcc tcccaggaac gccccaagag tgctgtgttt cctggcgagg
2761 ggaaggtcaa gatgagcgtg gaggagcaga ttgaccgaat gcggcggcac cagagtggct

Figure 24. (Page 37 of 46)

2821 ccatgaagga gaagcggagg agcctgcagc tcccggccag cccggccccc gaccccagtc
2881 cccggccagc ctacaaagtg gtgcgccgcc accgcagcat ccacgaggta gacatctcca
2941 acctggaggc agccctgcgg gcagaggagc ctggcgggca tgcctacgag acaccccggg
3001 aggaaattgc ccggcttcgc aaaatggagc tagagcccca gcattatgac gtggacatca
3061 ataaggagct ctccactcca gacaaagtcc tcatccctga acggtacatt gacctggagc
3121 ctgacactcc cctgagccct gaggagttga aggagaagca gaagaaggtg gagaggatca
3181 agacactcat tgccaaatcc agtatgcaga acgtggtgcc catcggcgag ggggactctg
3241 tggacgtgcc ccaggactca gagagccagc tgcaggagca ggagaagcgg attgaaatct
3301 cctgcgccct ggcgaccgag gcctcccgca ggggccgcat gctgtctgtg caatgtgcca
3361 ccccaagccc tcccacctcc cctgcttccc cggctcctcc agcaaacccc ctgtcgtctg
3421 aatccccacg gggcgccgac agcagctata ccatgcgggt ctgagctctg actgcaagcc
3481 ctggctgagg ccaatgctgt gaagctccac agagccacat tctgaagccg tcctctgccc
3541 acctgaggtc ctggctcccc accctggccc cctgcccctg cactcccatg ggaatgccgc
3601 agggagccag gctggggcca tgggctgctg ccagaggacc gtggatacct cagtgtccac
3661 acacccacca tgcccagccc tggagccatc actactcaca ccgtggtcct gggccagggc
3721 ctgagatgac agtggggagc accatcctca ttaatgtcca agtcacaggg agcctcagcc
3781 ttgccctggc tggggttgtg gtgactccag tggaacattc cctgatgggg gacatgccgt
3841 ggtggagaac acacctgtgg ctatcttatg tgaggactag aggtgaagag gagatggaca
3901 ctgcctctgg agccagcctg acaccaagga cagcacttgt catcatccct atcctcgtca
3961 gccccaccct gctgcctcag ctggacccag ggctttgaca caaacccagt gctttgctta
4021 tgggtgctcg ctggggtccg gtggagactg accaccctgc ttgagccaaa gacaaggtga
4081 tgagagatgg ggagaggcca ttggctccca gagggaacag tgctggctgt ggctagagaa
4141 cagcaggtct gtgcagtgtc tgagggcagg ttgggaaggg tagcagagag agagagacag
4201 aaagagagag agagagagag agagagagag agagagagag agagagatcc tcagagtgga
4261 aggaggggga agcagcagga cacattggca agtcaagcag gaaggaggga gatggaaagg
4321 ggatatcaga ttggtttccc ccggtggagc cttaggttag tgcccagtgc agtgccagac
4381 tgtctcctct gctcctccca cctcatccct aggaggaccc accagtggag cacatgcagc
4441 ctcagtggag atgcttggtg tggggatctg ggtgaagggg gttgagtagc gactgcctgg
4501 gagatggctg ttagtaggtc tgcgcctggt gtctgcctcg ccatcctggg gtaaggggca
4561 gagagaagga cttgtcttat gtagggtgtg gtcagccttg gggccttacc tacccagttc
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4681 tgaggagggg ggatgaggcc ttaatctggg aggcctatcc ccctatccca ggcatcccag
4741 acgaggactg gctgaggcta ggcgctctca tgatccacct gccccgggag ggcagcgggg
4801 aagacagaga aaagcaaaca cattcctcct cagctccacc cacctggaga cgaatgtagc
4861 cagagaggag gaaggaggga aactgaaaac accgtggccc ctcggccttc tctctgctag
4921 agttgccgct cagaggcttc agcctgactt ccagcggtcc caagaacacc tactaattcc
4981 tctccactcc ttcatggctg ggacagttac tggttcatat gcaagtaaag atgacaattt
5041 actcaac

Figure 24. (Page 38 of 46)

M61906 Human PI3-kinase, p85 subunit

1 tacaaccagg ctcaactgtt gcatggtagc agatttgcaa acatgagtgc tgaggggtac
61 cagtacagag cgctgtatga ttataaaaag gaaagagaag aagatattga cttgcacttg
121 ggtgacatat tgactgtgaa taaagggtcc ttagtagctc ttggattcag tgatggacag
181 gaagccaggc ctgaagaaat tggctggtta aatggctata atgaaaccac aggggaaagg
241 ggggactttc cgggaactta cgtagaatat attggaagga aaaaaatctc gcctcccaca
301 ccaaagcccc ggccacctcg gcctcttcct gttgcaccag gttcttcgaa aactgaagca
361 gatgttgaac aacaagcttt gactctcccg gatcttgcag agcagtttgc ccctcctgac
421 attgccccgc ctcttcttat caagctcgtg gaagccattg aaaagaaagg tctggaatgt
481 tcaactctat acagaacaca gagctccagc aacctggcag aattacgaca gcttcttgat
541 tgtgatacac cctccgtgga cttggaaatg atcgatgtgc acgttttggc tgacgctttc
601 aaacgctatc tcctggactt accaaatcct gtcattccag cagccgttta cagtgaaatg
661 atttctttag ctccagaagt acaaagctcc gaagaatata ttcagctatt gaagaagctt
721 attaggtcgc ctagcatacc tcatcagtat tggcttacgc ttcagtattt gttaaaacat
781 ttcttcaagc tctctcaaac ctccagcaaa aatctgttga atgcaagagt actctctgaa
841 attttcagcc ctatgctttt cagattctca gcagccagct ctgataatac tgaaaacctc
901 ataaaagtta tagaaatttt aatctcaact gaatggaatg aacgacagcc tgcaccagca
961 ctgcctccta aaccaccaaa acctactact gtagccaaca acggtatgaa taacaatatg
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1141 gattatactc ttacactaag gaaaggggga aataacaaat taatcaaaat atttcatcga
1201 gatgggaaat atggcttctc tgacccatta accttcagtt ctgtggttga attaataaac
1261 cactaccgga atgaatctct agctcagtat aatcccaaat tggatgtgaa attactttat
1321 ccagtatcca aataccaaca ggatcaagtt gtcaaagaag ataatattga agctgtaggg
1381 aaaaaattac atgaatataa cactcagttt caagaaaaaa gtcgagaata tgatagatta
1441 tatgaagaat atacccgcac atcccaggaa atccaaatga aaaggacagc tattgaagca
1501 tttaatgaaa ccataaaaat atttgaagaa cagtgccaga cccaagagcg gtacagcaaa
1561 gaatacatag aaaagtttaa acgtgaaggc aatgagaaag aaatacaaag gattatgcat
1621 aattatgata agttgaagtc tcgaatcagt gaaattattg acagtagaag aagattggaa
1681 gaagacttga agaagcaggc agctgagtat cgagaaattg acaaacgtat gaacagcatt
1741 aaaccagacc ttatccagct gagaaagacg agagaccaat acttgatgtg gttgactcaa
1801 aaaggtgttc ggcaaaagaa gttgaacgag tggttgggca atgaaaacac tgaagaccaa
1861 tattcactgg tggaagatga tgaagatttg ccccatcatg atgagaagac atggaatgtt
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1981 cttgtccggg agagcagtaa acagggctgc tatgcctgct ctgtagtggt ggacggcgaa
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2101 ttgtacagct ctctgaaaga actggtgcta cattaccaac acacctccct tgtgcagcac
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2281 gctcctctcc agtctgatct gtgaattgag ctgcagaaac gaagccatct ttctttggat
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2401 tgatgaccac acgttcctaa gctggagtgc ttatcccttc ttttttcttt tttctttggt
2461 ttaatttaaa gccacaacca catacaacac aaagagaaaa agaaatgcaa aaatctctgc
2521 gtgcagggac aaagaggcct ttaaccatgg tgcttgttaa tgctttctga agctttacca
2581 gctgaaagtt gggactctgg agagcggagg agagagaggc agaagaaccc tggcctgaga
2641 aggtttggtc cagcctggtt tagcctggat gttgctgtgc acggtggacc cagacacatc
2701 gcactgtgga ttatttcatt ttgtaacaaa tgaacgatat gtagcagaaa ggcacgtcca
2761 ctcacaaggg acgctttggg agaatgtcag ttcatgtatg ttcagaagaa attctgtcat

Figure 24. (Page 39 of 46)

2821 agaaagtgcc agaaagtgtt taacttgtca aaaaacaaaa acccagcaac agaaaaatgg
2881 agtttggaaa acaggactta aaatgacatt cagtatataa aatatgtaca taatattgga
2941 tgactaacta tcaaatagat ggatttgtat caataccaaa tagcttctgt tttgttttgc
3001 tgaaggctaa attcacagcg ctatgcaatt cttaattttc attaagttgt tatttcagtt
3061 ttaaatgtac cttcagaata agcttcccca ccccagtttt tgttgcttga aaatattgtt
3121 gtcccggatt tttgttaata ttcatttttg ttatcctttt ttaaaaataa atgtacagga
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3241 tgtacagagt acttgctgtt agcccaaggt taaaaagttc ataacagatt ttttttggac
3301 tgttttgttg ggcagtgcct gataagcttc aaagctgctt tattcaataa aaaaaaaacc
3361 cgaattcact gg

Figure 24. (Page 40 of 46)

J05582 Human mucin 1

1 ccgctccacc tctcaagcag ccagcgcctg cctgaatctg ttctgccccc tccccaccca
61 tttcaccacc accatgacac cgggcaccca gtctcctttc ttcctgctgc tgctcctcac
121 agtgcttaca gttgttacag gttctggtca tgcaagctct accccaggtg gagaaaagga
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241 gaccagcagc gtactctcca gccacagccc cggttcaggc tcctccacca ctcagggaca
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781 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
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961 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
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1141 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
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1261 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1321 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1381 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1441 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1501 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1561 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1621 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1681 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1741 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1801 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1861 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1921 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
1981 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2041 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2101 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2161 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2221 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2281 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2341 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2401 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2461 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2521 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2581 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2641 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2701 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2761 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca

Figure 24. (Page 41 of 46)

2821 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc ccccagccca
2881 tggtgtcacc tcggccccgg acaacaggcc cgccttgggc tccaccgccc ctccagtcca
2941 caatgtcacc tcggcctcag gctctgcatc aggctcagct tctactctgg tgcacaacgg
3001 cacctctgcc agggctacca caaccccagc cagcaagagc actccattct caattcccag
3061 ccaccactct gatactccta ccacccttgc cagccatagc accaagactg atgccagtag
3121 cactcaccat agctcggtac ctcctctcac ctcctccaat cacagcactt ctccccagtt
3181 gtctactggg gtctctttct ttttcctgtc ttttcacatt tcaaacctcc agtttaattc
3241 ctctctggaa gatcccagca ccgactacta ccaagagctg cagagagaca tttctgaaat
3301 gtttttgcag atttataaac aaggggttt tctgggcctc tccaatatta agttcaggcc
3361 aggatctgtg gtggtacaat tgactctggc cttccgagaa ggtaccatca atgtccacga
3421 cgtggagaca cagttcaatc agtataaaac ggaagcagcc tctcgatata acctgacgat
3481 ctcagacgtc agcgtgagtg atgtgccatt tcctttctct gcccagtctg gggctggggt
3541 gccaggctgg ggcatcgcgc tgctggtgct ggtctgtgtt ctggttgcgc tggccattgt
3601 ctatctcatt gccttggctg tctgtcagtg ccgccgaaag aactacgggc agctggacat
3661 ctttccagcc cgggatacct accatcctat gagcgagtac cccacctacc acacccatgg
3721 gcgctatgtg ccccctagca gtaccgatcg tagcccctat gagaaggttt ctgcaggtaa
3781 cggtggcagc agcctctctt acacaaaccc agcagtggca gccgcttctg ccaacttgta
3841 gggcacgtcg ccgctgagct gagtggccag ccagtgccat tccactccac tcaggttctt
3901 caggccagag cccctgcacc ctgtttgggc tggtgagctg ggagttcagg tgggctgctc
3961 acagcctcct tcagaggccc caccaatttc tcggacactt ctcagtgtgt ggaagctcat
4021 gtgggccccc gaggctcatg cctgggaagt gttgtggggg ctcccaggag gactggccca
4081 gagagccctg agatagcggg gatcctgaac tggactgaat aaaacgtggt ctcccactg

Figure 24. (Page 42 of 46)

M29366 Human Epidermal Growth Factor Receptor (ErbB3)

1 accaattcgc cagcggttca ggtggctctt gcctcgatgt cctagcctag gggcccccgg
61 gccggacttg gctgggctcc cttcaccctc tgcggagtca tgagggcgaa cgacgctctg
121 caggtgctgg gcttgctttt cagcctggcc cggggctccg aggtgggcaa ctctcaggca
181 gtgtgtcctg ggactctgaa tggcctgagt gtgaccggcg atgctgagaa ccaataccag
241 acactgtaca agctctacga gaggtgtgag gtggtgatgg ggaaccttga gattgtgctc
301 acgggacaca atgccgacct ctccttcctg cagtggattc gagaagtgac aggctatgtc
361 ctcgtggcca tgaatgaatt ctctactcta ccattgccca acctccgcgt ggtgcgaggg
421 acccaggtct acgatgggaa gtttgccatc ttcgtcatgt tgaactataa caccaactcc
481 agccacgctc tgcgccagct ccgcttgact cagctcaccg agattctgtc agggggtgtt
541 tatattgaga agaacgataa gctttgtcac atggacacaa ttgactggag ggacatcgtg
601 agggaccgag atgctgagat agtggtgaag gacaatggca gaagctgtcc cccctgtcat
661 gaggtttgca aggggcgatg ctggggtcct ggatcagaag actgccagac attgaccaag
721 accatctgtg ctcctcagtg taatggtcac tgctttgggc ccaaccccaa ccagtgctgc
781 catgatgagt gtgccggggg ctgctcaggc cctcaggaca cagactgctt tgcctgccgg
841 cacttcaatg acagtggagc ctgtgtacct cgctgtccac agcctcttgt ctacaacaag
901 ctaactttcc agctggaacc caatccccac accaagtatc agtatggagg agtttgtgta
961 gccagctgtc cccataactt tgtggtggat caaacatcct gtgtcagggc ctgtcctcct
1021 gacaagatgg aagtagataa aaatgggctc aagatgtgtg agccttgtgg gggactatgt
1081 cccaaagcct gtgagggaac aggctctggg agccgcttcc agactgtgga ctcgagcaac
1141 attgatggat ttgtgaactg caccaagatc ctgggcaacc tggactttct gatcaccggc
1201 ctcaatggag acccctggca caagatccct gccctggacc cagagaagct caatgtcttc
1261 cggacagtac gggagatcac aggttacctg aacatccagt cctggccgcc ccacatgcac
1321 aacttcagtg ttttttccaa tttgacaacc attggaggca gaagcctcta caaccggggc
1381 ttctcattgt tgatcatgaa gaacttgaat gtcacatctc tgggcttccg atccctgaag
1441 gaaattagtg ctgggcgtat ctatataagt gccaataggc agctctgcta ccaccactct
1501 ttgaactgga ccaaggtgct tcgggggcct acggaagagc gactagacat caagcataat
1561 cggccgcgca gagactgcgt ggcagagggc aaagtgtgtg acccactgtg ctcctctggg
1621 ggatgctggg gcccaggccc tggtcagtgc ttgtcctgtc gaaattatag ccgaggaggt
1681 gtctgtgtga cccactgcaa ctttctgaat ggggagcctc gagaatttgc ccatgaggcc
1741 gaatgcttct cctgccaccc ggaatgccaa cccatggagg gcactgccac atgcaatggc
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1981 gactgtttag gacaaacact ggtgctgatc ggcaaaaccc atctgacaat ggctttgaca
2041 gtgatagcag gattggtagt gattttcatg atgctgggcg gcacttttct ctactggcgt
2101 gggcgccgga ttcagaataa aagggctatg aggcgatact tggaacgggg tgagagcata
2161 gagcctctgg accccagtga gaaggctaac aaagtcttgg ccagaatctt caaagagaca
2221 gagctaagga agcttaaagt gcttggctcg ggtgtctttg gaactgtgca caaaggagtg
2281 tggatccctg agggtgaatc aatcaagatt ccagtctgca ttaaagtcat tgaggacaag
2341 agtggacggc agagttttca agctgtgaca gatcatatgc tggccattgg cagcctggac
2401 catgcccaca ttgtaaggct gctgggacta tgcccagggt catctctgca gcttgtcact
2461 caatatttgc ctctgggttc tctgctggat catgtgagac aacaccgggg ggcactgggg
2521 ccacagctgc tgctcaactg gggagtacaa attgccaagg gaatgtacta ccttgaggaa
2581 catggtatgg tgcatagaaa cctggctgcc cgaaacgtgc tactcaagtc acccagtcag
2641 gttcaggtgg cagattttgg tgtggctgac ctgctgcctc ctgatgataa gcagctgcta
2701 tacagtgagg ccaagactcc aattaagtgg atggcccttg agagtatcca ctttgggaaa
2761 tacacacacc agagtgatgt ctggagctat ggtgtgacag tttgggagtt gatgaccttc

Figure 24. (Page 43 of 46)

2821 ggggcagagc cctatgcagg gctacgattg gctgaagtac cagacctgct agagaagggg
2881 gagcggttgg cacagcccca gatctgcaca attgatgtct acatggtgat ggtcaagtgt
2941 tggatgattg atgagaacat tcgcccaacc tttaaagaac tagccaatga gttcaccagg
3001 atggcccgag acccaccacg gtatctggtc ataaagagag agagtgggcc tggaatagcc
3061 cctgggccag agccccatgg tctgacaaac aagaagctag aggaagtaga gctggagcca
3121 gaactagacc tagacctaga cttggaagca gaggaggaca acctggcaac caccacactg
3181 ggctccgccc tcagcctacc agttggaaca cttaatcggc cacgtgggag ccagagcctt
3241 ttaagtccat catctggata catgcccatg aaccagggta atcttgggga gtcttgccag
3301 gagtctgcag tttctgggag cagtgaacgg tgccccccgtc cagtctctct acacccaatg
3361 ccacggggat gcctggcatc agagtcatca gaggggcatg taacaggctc tgaggctgag
3421 ctccaggaga aagtgtcaat gtgtagaagc cggagcagga gccggagccc acggccacgc
3481 ggagatagcg cctaccattc ccagcgccac agtctgctga ctcctgttac cccactctcc
3541 ccacccgggt tagaggaaga ggatgtcaac ggttatgtca tgccagatac acacctcaaa
3601 ggtactccct cctcccggga aggcaccctt tcttcagtgg gtcttagttc tgtcctgggt
3661 actgaagaag aagatgaaga tgaggagtat gaatacatga accggaggag aaggcacagt
3721 ccacctcatc cccctaggcc aagttccctt gaggagctgg gttatgagta catggatgtg
3781 gggtcagacc tcagtgcctc tctgggcagc acacagagtt gcccactcca ccctgtaccc
3841 atcatgccca ctgcaggcac aactccagat gaagactatg aatatatgaa tcggcaacga
3901 gatggaggtg gtcctggggg tgattatgca gccatggggg cctgcccagc atctgagcaa
3961 gggtatgaag agatgagagc ttttcagggg cctggacatc aggccccccа tgtccattat
4021 gcccgcctaa aaactctacg tagcttagag gctacagact ctgcctttga taaccctgat
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4141 gtggcactca gggagcattt aatggcagct agtgccttta gagggtaccg tcttctccct
4201 attccctctc tctcccaggt cccagccccc tttccccagt cccagacaat tccattcaat
4261 ctttggaggc ttttaaacat tttgacacaa aattcttatg gtatgtagcc agctgtgcac
4321 tttcttctct ttcccaaccc caggaaaggt tttccttatt ttgtgtgctt tcccagtccc
4381 attcctcagc ttcttcacag gcactcctgg agatatgaag gattactctc catatccctt
4441 cctctcaggc tcttgactac ttggaactag gctcttatgt gtgcctttgt ttcccatcag
4501 actgtcaaga agaggaaagg gaggaaacct agcagaggaa agtgtaattt tggtttatga
4561 ctcttaaccc cctagaaaga cagaagctta aaatctgtga agaaagaggt taggagtaga
4621 tattgattac tatcataatt cagcacttaa ctatgagcca ggcatcatac taaacttcac
4681 ctacattatc tcacttagtc ctttatcatc cttaaaacaa ttctgtgaca tacatattat
4741 ctcattttac acaaagggaa gtcgggcatg gtggctcatg cctgtaatct cagcactttg
4801 ggaggctgag gcagaaggat tacctgaggc aaggagtttg agaccagctt agccaacata
4861 gtaagacccc catctcttt

Figure 24. (Page 44 of 46)

Homo sapiens gene for hepatitis C-associated microtubular aggregate protein p44

D28908 Exon 1 and 2

1 gaattctgaa tataggacac gaatttatga tccttagcaa tgtgaagtta gagaaggggt
61 tttattgtga aattgacaca ggttgtttta tatcttataa atgaagtctc ctcattttcc
121 tgtggtcaga agagaggggg caagcagaaa agcagaggaa caaatttgga ggctaaaata
181 acattctaca taaggaacta tactacagta gaattaattg atagcaggga ttaagagatg
241 taaatgaatt tgagatacat attctagagg tagaatgtgc aatacttttt gtatgtccat
301 atacagaaat tggttgcatt ttccttaaat aaaaagattt tttaaaagtc agtgagctgt
361 tatgttttct tccctctgac ttcaattcct tgattctttc aatttttta atataaattt
421 actgtctaaa agctggatca gcttatgctc ctttgttgag agaagttggc atgctgtcaa
481 gtgggctggg cacactgagt ttcagtttcc tttctctgag tctttgaagc ttcaaggctg
541 ctgaataatt tccttctccc attttgtgcc tgcctagcta tccagacaga gcagctaccc
601 tcagctctag ctgatactac agacagtaca acaggtaaat gtctttctgc ttttcatttt
661 tcctagctag cattagtctc tctctgtctc tctcaggtga cagtgtccat tgcaatctca
721 gtttttgttt taatttaaaa aacaataatt tatagtaaaa aattagctaa tgatttttt
781 gctttctgtt catcctttgt tttgtcattt tttgtattat gtagagtata taagaggcat
841 aaatgcaaat tttataacta catattatct gttttttaat atttaatgga aaatatatat
901 gatttgccac tagatcaaga agtatggcag tgacaactcg tttgacatgg ttgcacgaaa
961 agatcctgca aaatcatttt ggagggaagc ggcttagcct tctctataag ggtagtgtcc
1021 atggattccg taatggagtt ttgcttgaca gatgttgtaa tcaagggcct actctaacag
1081 tgatttatag tgaagatcat attattggag catatgcaga agagagttac caggaaggaa
1141 agtatgcttc catcatcctt tttgcacttc aagatactaa aatttcagaa tggaaactag
1201 gactatgtac accagaaaca ctgttttgtt gtgatgttac aaaatataac tccccaacta
1261 atttccagat agatggaaga aatagaaaag tgattatgga cttaaagaca atggaaaatc
1321 ttggacttgc tcaaaattgt actatctcta ttcaggatta tgaagttttt cgatgcgaag
1381 gtaggtttaa ttagataatc ctgtagagag ttctcccttg catgtttggt aggtttgaac
1441 caattcatct ctttaaggaa aaatgaactt ttcacttgtc aataatttgg atgattcaga
1501 ctgaaacctg gatacagatt gtttgctaag agacaaccat ggtcaataaa atgtatattt
1561 atgataagaa cccttaacgt aagatttatc ctcttagcac attttaagta c

D28909 Exon 3

1 gaattcactg atattcattc attcattcag ccaattattc gacaacttct aatctacatt
61 attctttgat tatttcccca gattcactgg atgaaagaaa gataaaaggg gtcattgagt
121 aagtcaatgt ttttaagatt ctattactct cttca

Figure 24. (Page 45 of 46)

D28910 Exon 4

1 tttgcgacct aacctcagtc aattgttaaa aacggtcatg tctaaacagg ctcaggaaga
61 gcttactgtc tgccttgaga acttatgaac catatggatc cctggttcaa caaatacgaa
121 ttctcctcct gggtccaatt ggagctccca agtccagctt tttcaactca gtgaggtctg
181 ttttccaagg gcatgtaacg catcaggctt tggtgggcac taatacaact gggatatctg
241 agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaat caattatatt
301 tcaaaagctt tt

D28911 Exon 5

1 ggccacctag cctttgcttc tctgttcaaa tcaattatat ttcaaaagcc ttttgcagat
61 caactttatt acatatagac ttcatctcaa tttataataa aaaatgaatc tttaaaattg
121 cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac
181 ctgccgttta ttctgtgtga ctcactgggg ctgagtgaga aagaaggcgg cctgtgcagg
241 gatgacatat tctatatctt gaacggtaac attcgtgata gataccaggt aatatttgac
301 taatgagaaa ttataactga tttttaaaat gcttattttt gtacaaatgt atcagcgttt
361 atcttcttaa attatacttg ctcaagatcc tttgtctctt ttagattttt tttttcaaaa
421 agaataaaaa catctcgagg gctcttc

D28912 Exon 6

1 ttgtgctcat aaatatttgt tgaattaata tcttgcttta tgtctacctt acagtttaat
61 cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac
121 agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctcctctcag
181 atgatagtaa agatcaaaag aattcaaagg gagttggtaa acgctggtga gtctcattcc
241 actttgctaa gggtaatacc actaagggta attgactaga ctgtatttta gaatgctttt
301 tggacaggat aaagaactta agtcattgca tatttcaatc t

D28913 Exon 7

1 gatctttcca aatctgaaat tgttccatag gttgcctatt acataattga tagttaaata
61 acttgaaaat actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg
121 tacatgtggc tttgctcact catgtggata gcatggattt gattacaaaa ggtgacctta
181 tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc cttcgtaaac
241 acattttctg gggtatgtta ctacaatcac atactagtgt gtataaaa

Figure 24. (Page 46 of 46)

D28914 Exon 8

1 ttttttcca atggaaatta ttgcaagttc ctacatcttg atattgcttt cataatttat
61 actaacataa aataatattt ttcactgttt tgcaatgtct ttttaatttc tgtattgcag
121 ctagaggaag tccaaagaaa acttggattt gctctttctg acatctcggt ggttagcaat
181 tattcctctg agtgggagct ggaccctgta aaggatgttc taattctttc tgctctgaga
241 cgaatgctat gggctgcaga tgacttctta gaggatttgc cttttgagca aataggtaga
301 tggtttggtg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttggatc
361 tattaaatac tg

D28915 Exon 9

1 cctctggttg cctttcctga gataatccac taagaatatt ttgtgtttct tttctcaggg
61 aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaaggttc
121 acgtaaattt cctcacatca cagaagatta aaattcagaa aggagaaaac acagaccaaa
181 gagaagtatc taagaccaaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata
241 gaacattgta gtacttgtaa ataactagaa ataacatgat ttagtcataa ttgtgaaaaa
301 taataataat ttttcttgga tttatgttct gtatctgtga aaaaataaat ttcttataaa
361 actcgggtct aacttgagag tgtgtgtgat tttggaaaaa ttatgatttg tcagcatctt
421 ctgatattca ctgctttcat cttaattttg ccttctgatt ttatttctaa agtatgtgat
481 ttt

Figure 25.

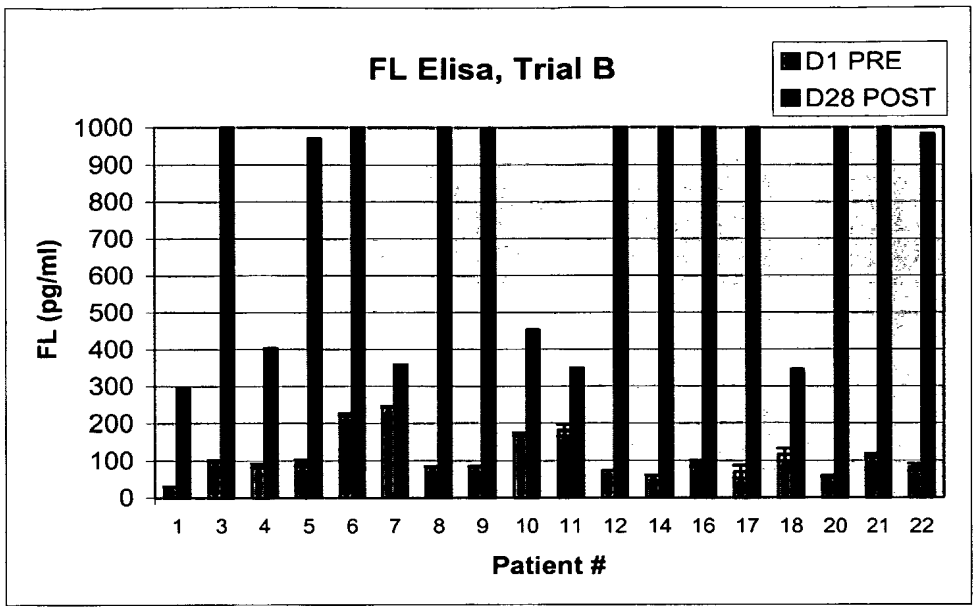

FL Elisa, Trial B
D1 PRE
D28 POST
FL (pg/ml)
1000
900
800
700
600
500
400
300
200
100
0
1 3 4 5 6 7 8 9 10 11 12 14 16 17 18 20 21 22
Patient #

Figure 26.

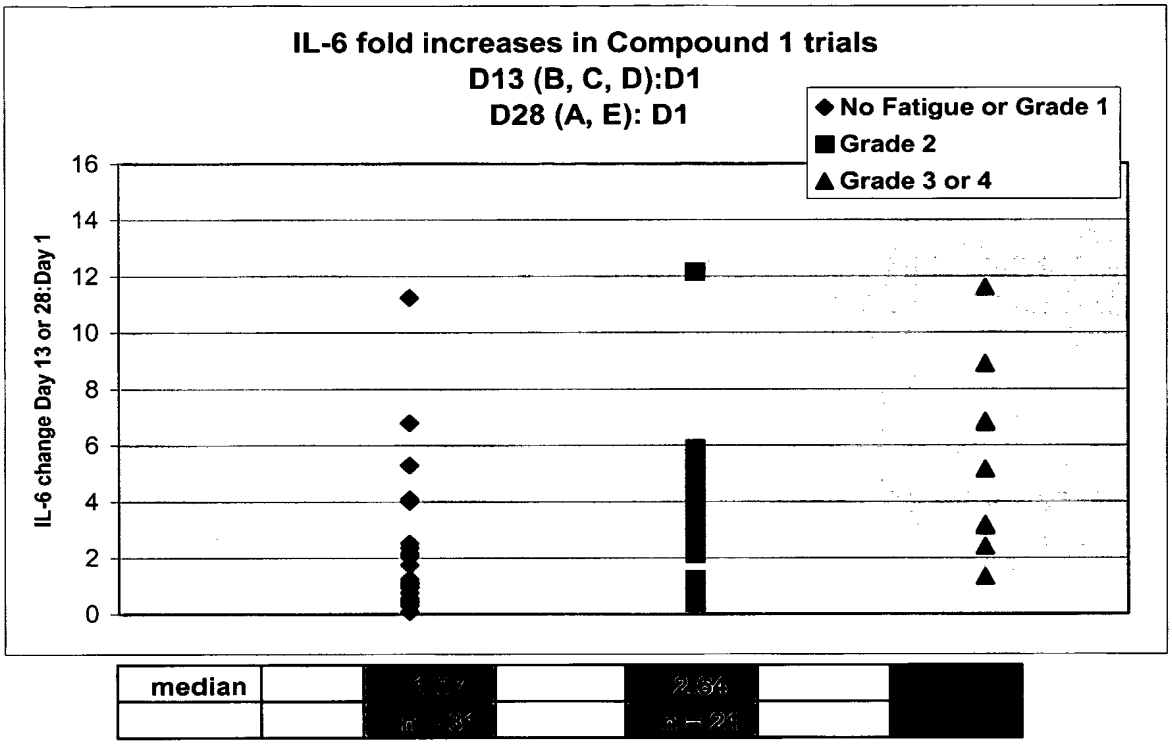

IL-6 fold increases in Compound 1 trials
D13 (B, C, D):D1
D28 (A, E): D1
No Fatigue or Grade 1
Grade 2
Grade 3 or 4
IL-6 change Day 13 or 28:Day 1
16
14
12
10
8
6
4
2
0
median

Figure 27.

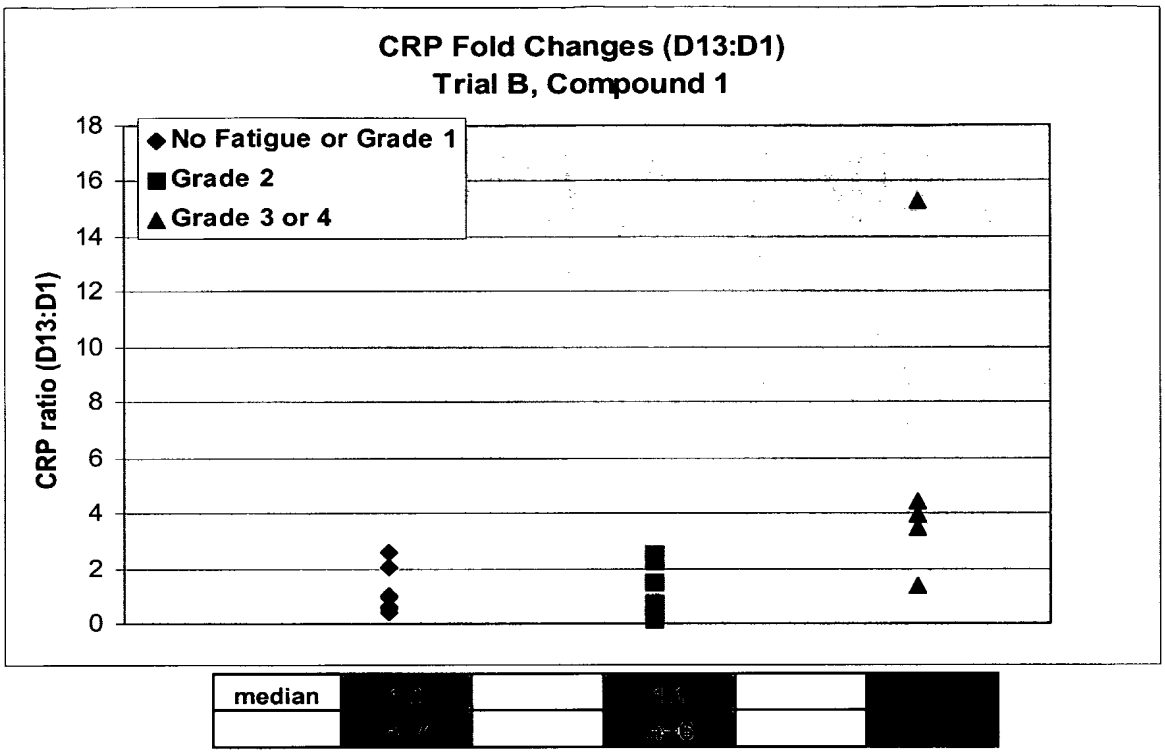
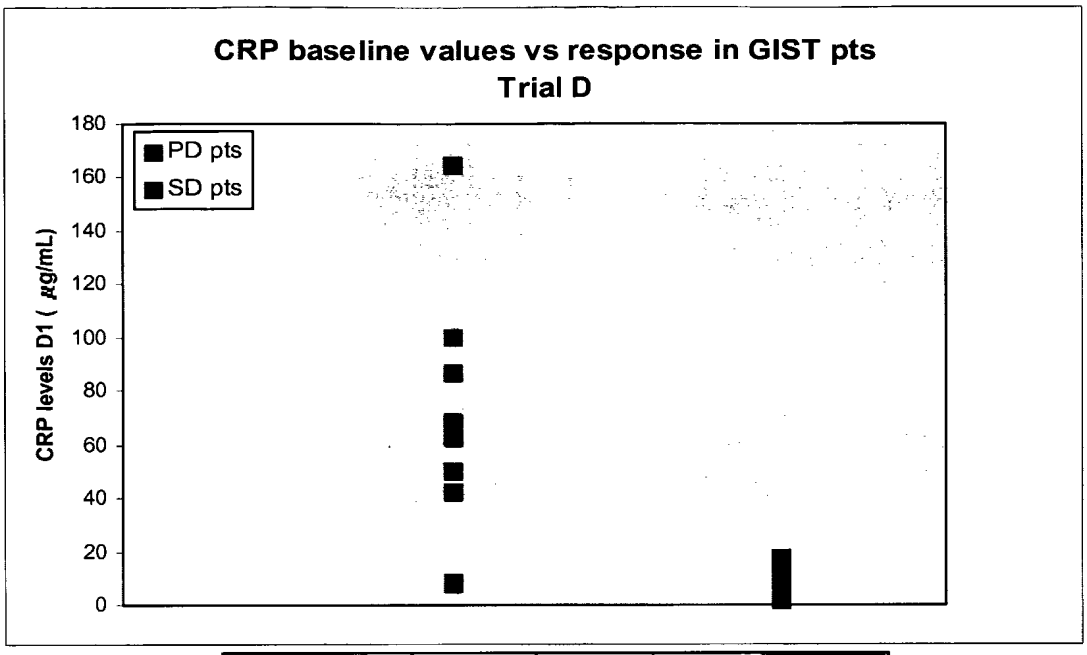

CRP Fold Changes (D13:D1)
Trial B, Compound 1
No Fatigue or Grade 1
Grade 2
Grade 3 or 4
CRP ratio (D13:D1)
0
2
4
6
8
10
12
14
16
18
median

Figure 28.



Median value	63.3			
	n=13			

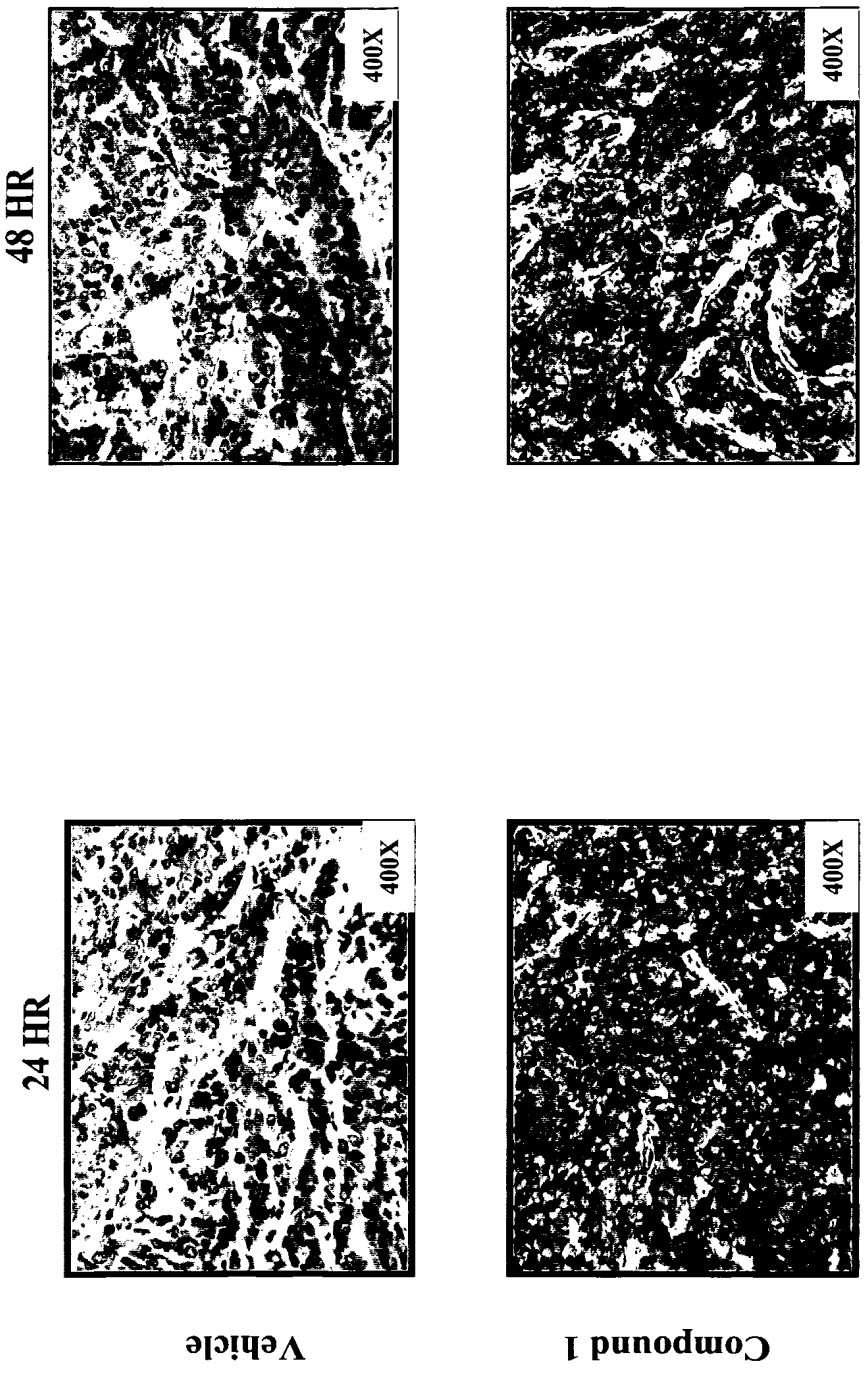


Figure 29.

SEQUENCE LISTING

<110> SUGEN, INC.

<120> NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE AND ACTIVITY IN MAMMALS

<130> 038602/1593

<140>
<141>

<150> 60/380,872
<151> 2002-05-17

<150> 60/448,922
<151> 2003-02-24

<150> 60/448,874
<151> 2003-02-24

<160> 185

<170> PatentIn Ver. 2.1

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<220>
<223> Description of Artificial Sequence: Primer

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ctggaagcct gtgaattcc 19

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gaatggctga ggctttcttg g 21

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gctgacttcg gaactaaagg agaa 24

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tgggacaggg aagacgatgt 20

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ctgcctcgac acacataaac ctt 23

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catctaagca tcagtgtgtg acca 24

<210> 13
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<210> 14
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<400> 16
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<210> 17
<211> 21
<212> DNA
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<220>
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<210> 18
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aagtgtcagc attctcaa 18

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<220>
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<400> 19
ccagtgttgt gaggatgcat atc 23

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agcgctcacc tttg 14

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<210> 26
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<220>
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attatgcttc atgtttcctg gctta 25

<210> 27
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<212> DNA
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<220>
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ccaaattaag aaatattata ctaatca 27

<210> 28
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<210> 29
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<212> DNA
<213> Artificial Sequence

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<400> 31
tcagccagct taaacccata caa 23

<210> 32
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tggcacgtat tagtttaaga tgaaagtag 29

<210> 33
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<400> 33
cttgttactg ctgattct 18

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<220>
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<400> 34
ttcagaggcc ccaccaatt 19

<210> 35
<211> 20
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<220>
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<400> 35
cccacatgag cttccacaca 20

<210> 36
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<220>
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<400> 36
tctcggacac ttctc 15

<210> 37
<211> 22

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 37
tgaggcaggg acaagtcttt ct 22

<210> 38
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<220>
<223> Description of Artificial Sequence: Primer

<400> 38
accctgactg aaggctcatg a 21

<210> 39
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<220>
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<400> 39
ctctttgaga ccccagtgc 19

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<212> DNA
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<220>
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<400> 40
tctaccgtcc ttgtcataac tttgtg 26

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<220>
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<400> 41
atgatgatgg gcccctgtt 19

<210> 42
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<220>
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<400> 42
cctttgccca agttg 15

<210> 43
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<220>
<223> Description of Artificial Sequence: Primer

<400> 43
tggacgtttt gtgatcgaag ag 22

<210> 44
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 44
aagtcaaggc ttctgtcttt tcttct 26

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<212> DNA
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cttgagaatc ctttccaacc 20

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<213> Homo sapiens

<400> 46
Asp Ile Tyr Ser Ser Phe Gly Phe Pro Arg
1 5 10

<210> 47
<211> 11
<212> PRT
<213> Homo sapiens

<400> 47
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg
1 5 10

<210> 48
<211> 114
<212> PRT
<213> Homo sapiens

<400> 48
Met Ser Leu Leu Ser Ser Arg Ala Ala Arg Val Pro Gly Pro Ser Ser
1 5 10 15

Ser Leu Cys Ala Leu Leu Val Leu Leu Leu Leu Leu Thr Gln Pro Gly
20 25 30

Pro Ile Ala Ser Ala Gly Pro Ala Ala Ala Val Leu Arg Glu Leu Arg
35 40 45

Cys Val Cys Leu Gln Thr Thr Gln Gly Val His Pro Lys Met Ile Ser
50 55 60

Asn Leu Gln Val Phe Ala Ile Gly Pro Gln Cys Ser Lys Val Glu Val
65 70 75 80

Val Ala Ser Leu Lys Asn Gly Lys Glu Ile Cys Leu Asp Pro Glu Ala
85 90 95

Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Gly Gly Asn Lys
100 105 110

Glu Asn

<210> 49
<211> 120
<212> PRT
<213> Homo sapiens

<400> 49
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Arg Val Thr Lys Asp Ala Glu Thr Glu Phe Met
20 25 30

Met Ser Lys Leu Pro Leu Glu Asn Pro Val Leu Leu Asp Arg Phe His
35 40 45

Ala Thr Ser Ala Asp Cys Cys Ile Ser Tyr Thr Pro Arg Ser Ile Pro
50 55 60

```
Cys Ser Leu Leu Glu Ser Tyr Phe Glu Thr Asn Ser Glu Cys Ser Lys
 65                  70                  75                  80

Pro Gly Val Ile Phe Leu Thr Lys Lys Gly Arg Arg Phe Cys Ala Asn
                 85                  90                  95

Pro Ser Asp Lys Gln Val Gln Val Cys Met Arg Met Leu Lys Leu Asp
            100                 105                 110

Thr Arg Ile Lys Thr Arg Lys Asn
        115                 120


<210> 50
<211> 902
<212> PRT
<213> Homo sapiens

<400> 50
Met Ser Glu Phe Arg Ile His His Asp Val Asn Glu Leu Leu Ser Leu
  1               5                  10                  15

Leu Arg Val His Gly Gly Asp Gly Ala Glu Val Tyr Ile Asp Leu Leu
             20                  25                  30

Gln Lys Asn Arg Thr Pro Tyr Val Thr Thr Thr Val Ser Ala His Ser
         35                  40                  45

Ala Lys Val Lys Ile Ala Glu Phe Ser Arg Thr Pro Glu Asp Phe Leu
     50                  55                  60

Lys Lys Tyr Asp Glu Leu Lys Ser Lys Asn Thr Arg Asn Leu Asp Pro
 65                  70                  75                  80

Leu Val Tyr Leu Leu Ser Lys Leu Thr Glu Asp Lys Glu Thr Leu Gln
                 85                  90                  95

Tyr Leu Gln Gln Asn Ala Lys Glu Arg Ala Glu Leu Ala Ala Ala Ala
            100                 105                 110

Val Gly Ser Ser Thr Thr Ser Ile Asn Val Pro Ala Ala Ala Ser Lys
        115                 120                 125

Ile Ser Met Gln Glu Leu Glu Glu Leu Arg Lys Gln Leu Gly Ser Val
    130                 135                 140

Ala Thr Gly Ser Thr Leu Gln Gln Ser Leu Glu Leu Lys Arg Lys Met
145                 150                 155                 160

Leu Arg Asp Lys Gln Asn Lys Lys Asn Ser Gly Gln His Leu Pro Ile
                165                 170                 175

Phe Pro Ala Trp Val Tyr Glu Arg Pro Ala Leu Ile Gly Asp Phe Leu
            180                 185                 190

Ile Gly Ala Gly Ile Ser Thr Asp Thr Ala Leu Pro Ile Gly Thr Leu
        195                 200                 205
```

```
Pro Leu Ala Ser Gln Glu Ser Ala Val Val Glu Asp Leu Leu Tyr Val
    210                 215                 220

Leu Val Gly Val Asp Gly Arg Tyr Val Ser Ala Gln Pro Leu Ala Gly
225                 230                 235                 240

Arg Gln Ser Arg Thr Phe Leu Val Asp Pro Asn Leu Asp Leu Ser Ile
                245                 250                 255

Arg Glu Leu Val His Arg Ile Leu Pro Val Ala Ala Ser Tyr Ser Ala
            260                 265                 270

Val Thr Arg Phe Ile Glu Glu Lys Ser Ser Phe Glu Tyr Gly Gln Val
        275                 280                 285

Asn His Ala Leu Ala Ala Ala Met Arg Thr Leu Val Lys Glu His Leu
    290                 295                 300

Ile Leu Val Ser Gln Leu Glu Gln Leu His Arg Gln Gly Leu Leu Ser
305                 310                 315                 320

Leu Gln Lys Leu Trp Phe Tyr Ile Gln Pro Ala Met Arg Thr Met Asp
                325                 330                 335

Ile Leu Ala Ser Leu Ala Thr Ser Val Asp Lys Gly Glu Cys Leu Gly
            340                 345                 350

Gly Ser Thr Leu Ser Leu Leu His Asp Arg Ser Phe Ser Tyr Thr Gly
        355                 360                 365

Asp Ser Gln Ala Gln Glu Leu Cys Leu Tyr Leu Thr Lys Ala Ala Ser
    370                 375                 380

Ala Pro Tyr Phe Glu Val Leu Glu Lys Trp Ile Tyr Arg Gly Ile Ile
385                 390                 395                 400

His Asp Pro Tyr Ser Glu Phe Met Val Glu Glu His Glu Leu Arg Lys
                405                 410                 415

Glu Arg Ile Gln Glu Asp Tyr Asn Asp Lys Tyr Trp Asp Gln Arg Tyr
            420                 425                 430

Thr Ile Val Gln Gln Gln Ile Pro Ser Phe Leu Gln Lys Met Ala Asp
        435                 440                 445

Lys Ile Leu Ser Thr Gly Lys Tyr Leu Asn Val Val Arg Glu Cys Gly
    450                 455                 460

His Asp Val Thr Cys Pro Val Ala Lys Glu Ile Ile Tyr Thr Leu Lys
465                 470                 475                 480

Glu Arg Ala Tyr Val Glu Gln Ile Glu Lys Ala Phe Asn Tyr Ala Ser
                485                 490                 495

Lys Val Leu Leu Asp Phe Leu Met Glu Glu Lys Glu Leu Val Ala His
            500                 505                 510
```

Leu Arg Ser Ile Lys Arg Tyr Phe Leu Met Asp Gln Gly Asp Phe Phe
515 520 525

Val His Phe Met Asp Leu Ala Glu Glu Glu Leu Arg Lys Pro Val Glu
530 535 540

Asp Ile Thr Pro Pro Arg Leu Glu Ala Leu Leu Glu Leu Ala Leu Arg
545 550 555 560

Met Ser Thr Ala Asn Thr Asp Pro Phe Lys Asp Asp Leu Lys Ile Asp
565 570 575

Leu Met Pro His Asp Leu Ile Thr Gln Leu Leu Arg Val Leu Ala Ile
580 585 590

Glu Thr Lys Gln Glu Lys Ala Met Ala His Ala Asp Pro Thr Glu Leu
595 600 605

Ala Leu Ser Gly Leu Glu Ala Phe Ser Phe Asp Tyr Ile Val Lys Trp
610 615 620

Pro Leu Ser Leu Ile Ile Asn Arg Lys Ala Leu Thr Arg Tyr Gln Met
625 630 635 640

Leu Phe Arg His Met Phe Tyr Cys Lys His Val Glu Arg Gln Leu Cys
645 650 655

Ser Val Trp Ile Ser Asn Lys Thr Ala Lys Gln His Ser Leu His Ser
660 665 670

Ala Gln Trp Phe Ala Gly Ala Phe Thr Leu Arg Gln Arg Met Leu Asn
675 680 685

Phe Val Gln Asn Ile Gln Tyr Tyr Met Met Phe Glu Val Met Glu Pro
690 695 700

Thr Trp His Ile Leu Glu Lys Asn Leu Lys Ser Ala Ser Asn Ile Asp
705 710 715 720

Asp Val Leu Gly His His Thr Gly Phe Leu Asp Thr Cys Leu Lys Asp
725 730 735

Cys Met Leu Thr Asn Pro Glu Leu Leu Lys Val Phe Ser Lys Leu Met
740 745 750

Ser Val Cys Val Met Phe Thr Asn Cys Met Gln Lys Phe Thr Gln Ser
755 760 765

Met Lys Leu Asp Gly Glu Leu Gly Gly Gln Thr Leu Glu His Ser Thr
770 775 780

Val Leu Gly Leu Pro Ala Gly Ala Glu Glu Arg Ala Arg Lys Glu Leu
785 790 795 800

Ala Arg Lys His Leu Ala Glu His Ala Asp Thr Val Gln Leu Val Ser
805 810 815

```
Gly Phe Glu Ala Thr Ile Asn Lys Phe Asp Lys Asn Phe Ser Ala His
            820                 825                 830

Leu Leu Asp Leu Leu Ala Arg Leu Ser Ile Tyr Ser Thr Ser Asp Cys
        835                 840                 845

Glu His Gly Met Ala Ser Val Ile Ser Arg Leu Asp Phe Asn Gly Phe
    850                 855                 860

Tyr Thr Glu Arg Leu Glu Arg Leu Ser Ala Glu Arg Ser Gln Lys Ala
865                 870                 875                 880

Thr Pro Gln Val Pro Val Leu Arg Gly Pro Pro Ala Pro Ala Pro Arg
                885                 890                 895

Val Ala Val Thr Ala Gln
            900
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<210> 51
<211> 252
<212> PRT
<213> Homo sapiens

<400> 51

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Met Arg Ala Pro Leu Leu Pro Pro Ala Pro Val Val Leu Ser Leu Leu
  1               5                  10                  15

Ile Leu Gly Ser Gly His Tyr Ala Ala Gly Leu Asp Leu Asn Asp Thr
             20                  25                  30

Tyr Ser Gly Lys Arg Glu Pro Phe Ser Gly Asp His Ser Ala Asp Gly
         35                  40                  45

Phe Glu Val Thr Ser Arg Ser Glu Met Ser Ser Gly Ser Glu Ile Ser
     50                  55                  60

Pro Val Ser Glu Met Pro Ser Ser Ser Glu Pro Ser Ser Gly Ala Asp
 65                  70                  75                  80

Tyr Asp Tyr Ser Glu Glu Tyr Asp Asn Glu Pro Gln Ile Pro Gly Tyr
                 85                  90                  95

Ile Val Asp Asp Ser Val Arg Val Glu Gln Val Val Lys Pro Pro Gln
            100                 105                 110

Asn Lys Thr Glu Ser Glu Asn Thr Ser Asp Lys Pro Lys Arg Lys Lys
        115                 120                 125

Lys Gly Gly Lys Asn Gly Lys Asn Arg Arg Asn Arg Lys Lys Lys Asn
    130                 135                 140

Pro Cys Asn Ala Glu Phe Gln Asn Phe Cys Ile His Gly Glu Cys Lys
145                 150                 155                 160

Tyr Ile Glu His Leu Glu Ala Val Thr Cys Lys Cys Gln Gln Glu Tyr
                165                 170                 175
```

```
Phe Gly Glu Arg Cys Gly Glu Lys Ser Met Lys Thr His Ser Met Ile
            180                 185                 190

Asp Ser Ser Leu Ser Lys Ile Ala Leu Ala Ala Ile Ala Ala Phe Met
        195                 200                 205

Ser Ala Val Ile Leu Thr Ala Val Ala Val Ile Thr Val Gln Leu Arg
    210                 215                 220

Arg Gln Tyr Val Arg Lys Tyr Glu Gly Glu Ala Glu Glu Arg Lys Lys
225                 230                 235                 240

Leu Arg Gln Glu Asn Gly Asn Val His Ala Ile Ala
                245                 250


<210> 52
<211> 271
<212> PRT
<213> Homo sapiens

<400> 52
Met Ala Lys Val Pro Asp Met Phe Glu Asp Leu Lys Asn Cys Tyr Ser
  1               5                  10                  15

Glu Asn Glu Glu Asp Ser Ser Ser Ile Asp His Leu Ser Leu Asn Gln
            20                  25                  30

Lys Ser Phe Tyr His Val Ser Tyr Gly Pro Leu His Glu Gly Cys Met
        35                  40                  45

Asp Gln Ser Val Ser Leu Ser Ile Ser Glu Thr Ser Lys Thr Ser Lys
    50                  55                  60

Leu Thr Phe Lys Glu Ser Met Val Val Val Ala Thr Asn Gly Lys Val
65                  70                  75                  80

Leu Lys Lys Arg Arg Leu Ser Leu Ser Gln Ser Ile Thr Asp Asp Asp
                85                  90                  95

Leu Glu Ala Ile Ala Asn Asp Ser Glu Glu Glu Ile Ile Lys Pro Arg
            100                 105                 110

Ser Ala Pro Phe Ser Phe Leu Ser Asn Val Lys Tyr Asn Phe Met Arg
        115                 120                 125

Ile Ile Lys Tyr Glu Phe Ile Leu Asn Asp Ala Leu Asn Gln Ser Ile
    130                 135                 140

Ile Arg Ala Asn Asp Gln Tyr Leu Thr Ala Ala Ala Leu His Asn Leu
145                 150                 155                 160

Asp Glu Ala Val Lys Phe Asp Met Gly Ala Tyr Lys Ser Ser Lys Asp
                165                 170                 175

Asp Ala Lys Ile Thr Val Ile Leu Arg Ile Ser Lys Thr Gln Leu Tyr
            180                 185                 190
```

```
Val Thr Ala Gln Asp Glu Asp Gln Pro Val Leu Leu Lys Glu Met Pro
        195                 200                 205

Glu Ile Pro Lys Thr Ile Thr Gly Ser Glu Thr Asn Leu Leu Phe Phe
    210                 215                 220

Trp Glu Thr His Gly Thr Lys Asn Tyr Phe Thr Ser Val Ala His Pro
225                 230                 235                 240

Asn Leu Phe Ile Ala Thr Lys Gln Asp Tyr Trp Val Cys Leu Ala Gly
                245                 250                 255

Gly Pro Pro Ser Ile Thr Asp Phe Gln Ile Leu Glu Asn Gln Ala
            260                 265                 270


<210> 53
<211> 269
<212> PRT
<213> Homo sapiens

<400> 53
Met Ala Glu Val Pro Glu Leu Ala Ser Glu Met Met Ala Tyr Tyr Ser
  1               5                  10                  15

Gly Asn Glu Asp Asp Leu Phe Phe Glu Ala Asp Gly Pro Lys Gln Met
             20                  25                  30

Lys Cys Ser Phe Gln Asp Leu Asp Leu Cys Pro Leu Asp Gly Gly Ile
         35                  40                  45

Gln Leu Arg Ile Ser Asp His His Tyr Ser Lys Gly Phe Arg Gln Ala
     50                  55                  60

Ala Ser Val Val Val Ala Met Asp Lys Leu Arg Lys Met Leu Val Pro
 65                  70                  75                  80

Cys Pro Gln Thr Phe Gln Glu Asn Asp Leu Ser Thr Phe Phe Pro Phe
                85                  90                  95

Ile Phe Glu Glu Glu Pro Ile Phe Phe Asp Thr Trp Asp Asn Glu Ala
            100                 105                 110

Tyr Val His Asp Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp
        115                 120                 125

Ser Gln Gln Lys Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala
    130                 135                 140

Leu His Leu Gln Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met
145                 150                 155                 160

Ser Phe Val Gln Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu
                165                 170                 175

Gly Leu Lys Glu Lys Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp
            180                 185                 190
```

```
Lys Pro Thr Leu Gln Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys
        195                 200                 205

Lys Lys Met Glu Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn
    210                 215                 220

Lys Leu Glu Phe Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr
225                 230                 235                 240

Ser Gln Ala Glu Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly
                245                 250                 255

Gln Asp Ile Thr Asp Phe Thr Met Gln Phe Val Ser Ser
            260                 265
```

<210> 54
<211> 153
<212> PRT
<213> Homo sapiens

<400> 54

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Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
  1               5                  10                  15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
             20                  25                  30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
         35                  40                  45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
     50                  55                  60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
 65                  70                  75                  80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                 85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145                 150
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<210> 55
<211> 125
<212> PRT
<213> Homo sapiens

<400> 55
Met Lys Lys Ser Gly Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val
1 5 10 15

Leu Ile Gly Val Gln Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser
20 25 30

Cys Ile Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp
35 40 45

Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile
50 55 60

Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala
65 70 75 80

Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys
85 90 95

Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys
100 105 110

Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr
115 120 125

<210> 56
<211> 210
<212> PRT
<213> Homo sapiens

<400> 56
Met Leu Pro Leu Pro Ser Cys Ser Leu Pro Ile Leu Leu Leu Phe Leu
1 5 10 15

Leu Pro Ser Val Pro Ile Glu Ser Gln Pro Pro Pro Ser Thr Leu Pro
20 25 30

Pro Phe Leu Ala Pro Glu Trp Asp Leu Leu Ser Pro Arg Val Val Leu
35 40 45

Ser Arg Gly Ala Pro Ala Gly Pro Pro Leu Leu Phe Leu Leu Glu Ala
50 55 60

Gly Ala Phe Arg Glu Ser Ala Gly Ala Pro Ala Asn Arg Ser Arg Arg
65 70 75 80

Gly Val Ser Glu Thr Ala Pro Ala Ser Arg Arg Gly Glu Leu Ala Val
85 90 95

Cys Asp Ala Val Ser Gly Trp Val Thr Asp Arg Arg Thr Ala Val Asp
100 105 110

Leu Arg Gly Arg Glu Val Glu Val Leu Gly Glu Val Pro Ala Ala Gly
115 120 125

Gly Ser Pro Leu Arg Gln Tyr Phe Phe Glu Thr Arg Cys Lys Ala Asp
130 135 140

```
Asn Ala Glu Glu Gly Gly Pro Gly Ala Gly Gly Gly Gly Cys Arg Gly
145                 150                 155                 160

Val Asp Arg Arg His Trp Val Ser Glu Cys Lys Ala Lys Gln Ser Tyr
                165                 170                 175

Val Arg Ala Leu Thr Ala Asp Ala Gln Gly Arg Val Gly Trp Arg Trp
            180                 185                 190

Ile Arg Ile Asp Thr Ala Cys Val Cys Thr Leu Leu Ser Arg Thr Gly
        195                 200                 205

Arg Ala
    210
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<210> 57
<211> 259
<212> PRT
<213> Homo sapiens

<400> 57

```
Met Ser Glu Val Pro Val Ala Arg Val Trp Leu Val Leu Leu Leu Leu
  1               5                  10                  15

Thr Val Gln Val Gly Val Thr Ala Gly Ala Pro Trp Gln Cys Ala Pro
             20                  25                  30

Cys Ser Ala Glu Lys Leu Ala Leu Cys Pro Pro Val Ser Ala Ser Cys
         35                  40                  45

Ser Glu Val Thr Arg Ser Ala Gly Cys Gly Cys Cys Pro Met Cys Ala
     50                  55                  60

Leu Pro Leu Gly Ala Ala Cys Gly Val Ala Thr Ala Arg Cys Ala Arg
 65                  70                  75                  80

Gly Leu Ser Cys Arg Ala Leu Pro Gly Glu Gln Gln Pro Leu His Ala
                85                  90                  95

Leu Thr Arg Gly Gln Gly Ala Cys Val Gln Glu Ser Asp Ala Ser Ala
            100                 105                 110

Pro His Ala Ala Glu Ala Gly Ser Pro Glu Ser Pro Glu Ser Thr Glu
        115                 120                 125

Ile Thr Glu Glu Glu Leu Leu Asp Asn Phe His Leu Met Ala Pro Ser
    130                 135                 140

Glu Glu Asp His Ser Ile Leu Trp Asp Ala Ile Ser Thr Tyr Asp Gly
145                 150                 155                 160

Ser Lys Ala Leu His Val Thr Asn Ile Lys Lys Trp Lys Glu Pro Cys
                165                 170                 175

Arg Ile Glu Leu Tyr Arg Val Val Glu Ser Leu Ala Lys Ala Gln Glu
            180                 185                 190
```

```
Thr Ser Gly Glu Glu Ile Ser Lys Phe Tyr Leu Pro Asn Cys Asn Lys
        195                 200                 205

Asn Gly Phe Tyr His Ser Arg Gln Cys Glu Thr Ser Met Asp Gly Glu
    210                 215                 220

Ala Gly Leu Cys Trp Cys Val Tyr Pro Trp Asn Gly Lys Arg Ile Pro
225                 230                 235                 240

Gly Ser Pro Glu Ile Arg Gly Asp Pro Asn Cys Gln Ile Tyr Phe Asn
                245                 250                 255

Val Gln Asn
```

<210> 58
<211> 107
<212> PRT
<213> Homo sapiens

<400> 58

```
Met Ala Arg Ala Thr Leu Ser Ala Ala Pro Ser Asn Pro Arg Leu Leu
  1               5                  10                  15

Arg Val Ala Leu Leu Leu Leu Leu Leu Val Ala Ala Ser Arg Arg Ala
             20                  25                  30

Ala Gly Ala Pro Leu Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr
         35                  40                  45

Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Lys Val Lys Ser
     50                  55                  60

Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn
 65                  70                  75                  80

Gly Gln Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Lys Lys Ile
                 85                  90                  95

Ile Glu Lys Met Leu Lys Asn Gly Lys Ser Asn
            100                 105
```

<210> 59
<211> 455
<212> PRT
<213> Homo sapiens

<400> 59

```
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
  1               5                  10                  15

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
             20                  25                  30
```

```
His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
         35                  40                  45

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
     50                  55                  60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
 65                  70                  75                  80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
                 85                  90                  95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
            100                 105                 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
        115                 120                 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
    130                 135                 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145                 150                 155                 160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205

Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu
    210                 215                 220

Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys
225                 230                 235                 240

Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu
                245                 250                 255

Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser
            260                 265                 270

Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val
        275                 280                 285

Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys
    290                 295                 300

Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly
305                 310                 315                 320

Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn
                325                 330                 335
```

```
Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
            340                 345                 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
        355                 360                 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
    370                 375                 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
385                 390                 395                 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
                405                 410                 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
            420                 425                 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
        435                 440                 445

Pro Ala Pro Ser Leu Leu Arg
    450                 455


<210> 60
<211> 235
<212> PRT
<213> Homo sapiens

<400> 60
Met Thr Val Leu Ala Pro Ala Trp Ser Pro Thr Thr Tyr Leu Leu Leu
  1               5                  10                  15

Leu Leu Leu Leu Ser Ser Gly Leu Ser Gly Thr Gln Asp Cys Ser Phe
             20                  25                  30

Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
         35                  40                  45

Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
     50                  55                  60

Gln Asp Glu Glu Leu Cys Gly Ala Leu Trp Arg Leu Val Leu Ala Gln
 65                  70                  75                  80

Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
                 85                  90                  95

Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
            100                 105                 110

Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
        115                 120                 125

Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
    130                 135                 140
```

```
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
145                 150                 155                 160

Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala
                165                 170                 175

Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu Leu Leu Leu Leu Leu Leu
            180                 185                 190

Pro Val Gly Leu Leu Leu Leu Ala Ala Ala Trp Cys Leu His Trp Gln
        195                 200                 205

Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly Glu Gln Val Pro Pro Val
    210                 215                 220

Pro Ser Pro Gln Asp Leu Leu Leu Val Glu His
225                 230                 235


<210> 61
<211> 212
<212> PRT
<213> Homo sapiens

<400> 61
Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu
  1               5                  10                  15

Gly Leu Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro
             20                  25                  30

Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr
         35                  40                  45

Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile
     50                  55                  60

Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser
 65                  70                  75                  80

Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala
                 85                  90                  95

Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu
            100                 105                 110

Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr
        115                 120                 125

Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln
    130                 135                 140

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn
145                 150                 155                 160

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu
                165                 170                 175
```

```
Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His
            180                 185                 190

Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala
        195                 200                 205

Leu Arg Gln Met
    210
```

<210> 62
<211> 99
<212> PRT
<213> Homo sapiens

<400> 62

```
Met Lys Val Ser Ala Ala Leu Leu Cys Leu Leu Leu Ile Ala Ala Thr
  1               5                  10                  15

Phe Ile Pro Gln Gly Leu Ala Gln Pro Asp Ala Ile Asn Ala Pro Val
             20                  25                  30

Thr Cys Cys Tyr Asn Phe Thr Asn Arg Lys Ile Ser Val Gln Arg Leu
         35                  40                  45

Ala Ser Tyr Arg Arg Ile Thr Ser Ser Lys Cys Pro Lys Glu Ala Val
     50                  55                  60

Ile Phe Lys Thr Ile Val Ala Lys Glu Ile Cys Ala Asp Pro Lys Gln
 65                  70                  75                  80

Lys Trp Val Gln Asp Ser Met Asp His Leu Asp Lys Gln Thr Gln Thr
                 85                  90                  95

Pro Lys Thr
```

<210> 63
<211> 233
<212> PRT
<213> Homo sapiens

<400> 63

```
Met Ser Thr Glu Ser Met Ile Arg Asp Val Glu Leu Ala Glu Glu Ala
  1               5                  10                  15

Leu Pro Lys Lys Thr Gly Gly Pro Gln Gly Ser Arg Arg Cys Leu Phe
             20                  25                  30

Leu Ser Leu Phe Ser Phe Leu Ile Val Ala Gly Ala Thr Thr Leu Phe
         35                  40                  45

Cys Leu Leu His Phe Gly Val Ile Gly Pro Gln Arg Glu Glu Phe Pro
     50                  55                  60

Arg Asp Leu Ser Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser
 65                  70                  75                  80
```

```
Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
                85                  90                  95

Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu
            100                 105                 110

Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser
        115                 120                 125

Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly
    130                 135                 140

Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala
145                 150                 155                 160

Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro
                165                 170                 175

Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu
            180                 185                 190

Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu
        195                 200                 205

Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly
    210                 215                 220

Gln Val Tyr Phe Gly Ile Ile Ala Leu
225                 230
```

<210> 64
<211> 94
<212> PRT
<213> Homo sapiens

<400> 64

```
Met Ala Pro Leu Lys Met Leu Ala Leu Val Thr Leu Leu Leu Gly Ala
  1               5                  10                  15

Ser Leu Gln His Ile His Ala Ala Arg Gly Thr Asn Val Gly Arg Glu
             20                  25                  30

Cys Cys Leu Glu Tyr Phe Lys Gly Ala Ile Pro Leu Arg Lys Leu Lys
         35                  40                  45

Thr Trp Tyr Gln Thr Ser Glu Asp Cys Ser Arg Asp Ala Ile Val Phe
     50                  55                  60

Val Thr Val Gln Gly Arg Ala Ile Cys Ser Asp Pro Asn Asn Lys Arg
 65                  70                  75                  80

Val Lys Asn Ala Val Lys Tyr Leu Gln Ser Leu Glu Arg Ser
                85                  90
```

<210> 65
<211> 267
<212> PRT
<213> Homo sapiens

<400> 65

```
Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
  1               5                  10                  15

Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
             20                  25                  30

Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
         35                  40                  45

Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
     50                  55                  60

Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
 65                  70                  75                  80

Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
                 85                  90                  95

Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
            100                 105                 110

Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
        115                 120                 125

Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
    130                 135                 140

Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145                 150                 155                 160

Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
                165                 170                 175

Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
            180                 185                 190

Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
        195                 200                 205

Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
    210                 215                 220

Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
225                 230                 235                 240

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
                245                 250                 255

Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
            260                 265
```

<210> 66
<211> 707
<212> PRT
<213> Homo sapiens

<400> 66

```
Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
  1               5                  10                  15

Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
             20                  25                  30

Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
         35                  40                  45

Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
     50                  55                  60

Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
 65                  70                  75                  80

Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
                 85                  90                  95

Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
            100                 105                 110

Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
        115                 120                 125

Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
    130                 135                 140

Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145                 150                 155                 160

Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
                165                 170                 175

Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
            180                 185                 190

Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
        195                 200                 205

Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
    210                 215                 220

Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225                 230                 235                 240

Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
                245                 250                 255

Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
            260                 265                 270
```

```
Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
        275                 280                 285

Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
    290                 295                 300

Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305                 310                 315                 320

Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
                325                 330                 335

Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
            340                 345                 350

Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
        355                 360                 365

Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
    370                 375                 380

Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
385                 390                 395                 400

His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
                405                 410                 415

Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
            420                 425                 430

Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
        435                 440                 445

Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
    450                 455                 460

Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465                 470                 475                 480

Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                485                 490                 495

Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
            500                 505                 510

Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
        515                 520                 525

Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
    530                 535                 540

Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545                 550                 555                 560

Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
                565                 570                 575
```

```
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
            580                 585                 590

Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
        595                 600                 605

Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
    610                 615                 620

Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625                 630                 635                 640

Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                645                 650                 655

Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
            660                 665                 670

Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
        675                 680                 685

Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
    690                 695                 700

Pro Glu Asp
705
```

<210> 67
<211> 167
<212> PRT
<213> Homo sapiens

<400> 67

```
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
  1               5                  10                  15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
             20                  25                  30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
         35                  40                  45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
     50                  55                  60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
 65                  70                  75                  80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
                 85                  90                  95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
            100                 105                 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
        115                 120                 125
```

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145 150 155 160

Leu Asp Leu Ser Pro Gly Cys
165

<210> 68
<211> 2619
<212> DNA
<213> Homo sapiens

<400> 68
gactcctagg ggcttgcaga cctagtggga gagaaagaac atcgcagcag ccaggcagaa 60
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gcctcagggc ttttcggagc ctggatcctc aaggaacaag tagacctggc cgcggggagt 180
ggggagggaa ggggtgtcta ttgggcaaca gggcggcaaa gccctgaata aaggggcgca 240
gggcaggcgc aagtgcagag ccttcgtttg ccaagtcgcc tccagaccgc agacatgaaa 300
cttgtcttcc tcgtcctgct gttcctcggg gccctcggac tgtgtctggc tggccgtagg 360
agaaggagtg ttcagtggtg cgccgtatcc caacccgagg ccacaaaatg cttccaatgg 420
caaaggaata tgagaaaagt gcgtggccct cctgtcagct gcataaagag agactccccc 480
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<210> 69
<211> 711
<212> PRT
<213> Homo sapiens

<400> 69

Met	Lys	Leu	Val	Phe	Leu	Val	Leu	Leu	Phe	Leu	Gly	Ala	Leu	Gly	Leu
1				5					10					15	
Cys	Leu	Ala	Gly	Arg	Arg	Arg	Arg	Ser	Val	Gln	Trp	Cys	Ala	Val	Ser
		20					25					30			
Gln	Pro	Glu	Ala	Thr	Lys	Cys	Phe	Gln	Trp	Gln	Arg	Asn	Met	Arg	Lys
	35					40					45				
Val	Arg	Gly	Pro	Pro	Val	Ser	Cys	Ile	Lys	Arg	Asp	Ser	Pro	Ile	Gln
50					55					60					
Cys	Ile	Gln	Ala	Ile	Ala	Glu	Asn	Arg	Ala	Asp	Ala	Val	Thr	Leu	Asp
65				70					75					80	
Gly	Gly	Phe	Ile	Tyr	Glu	Ala	Gly	Leu	Ala	Pro	Tyr	Lys	Leu	Arg	Pro
			85					90					95		
Val	Ala	Ala	Glu	Val	Tyr	Gly	Thr	Glu	Arg	Gln	Pro	Arg	Thr	His	Tyr
		100					105					110			
Tyr	Ala	Val	Ala	Val	Val	Lys	Lys	Gly	Gly	Ser	Phe	Gln	Leu	Asn	Glu
	115					120					125				
Leu	Gln	Gly	Leu	Lys	Ser	Cys	His	Thr	Gly	Leu	Arg	Arg	Thr	Ala	Gly
130					135					140					
Trp	Asn	Val	Pro	Thr	Gly	Thr	Leu	Arg	Pro	Phe	Leu	Asn	Trp	Thr	Gly
145				150					155					160	
Pro	Pro	Glu	Pro	Ile	Glu	Ala	Ala	Val	Ala	Arg	Phe	Phe	Ser	Ala	Ser
			165					170					175		
Cys	Val	Pro	Gly	Ala	Asp	Lys	Gly	Gln	Phe	Pro	Asn	Leu	Cys	Arg	Leu
		180					185					190			
Cys	Ala	Gly	Thr	Gly	Glu	Asn	Lys	Cys	Ala	Phe	Ser	Ser	Gln	Glu	Pro
	195					200					205				
Tyr	Phe	Ser	Tyr	Ser	Gly	Ala	Phe	Lys	Cys	Leu	Arg	Asp	Gly	Ala	Gly
210					215					220					
Asp	Val	Ala	Phe	Ile	Arg	Glu	Ser	Thr	Val	Phe	Glu	Asp	Leu	Ser	Asp
225				230					235					240	
Glu	Ala	Glu	Arg	Asp	Glu	Tyr	Glu	Leu	Leu	Cys	Pro	Asp	Asn	Thr	Arg
			245					250					255		

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Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
           260                 265                 270

His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
       275                 280                 285

Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
   290                 295                 300

Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
305                 310                 315                 320

Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
                325                 330                 335

Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
           340                 345                 350

Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
       355                 360                 365

Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
   370                 375                 380

Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
385                 390                 395                 400

Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
                405                 410                 415

Gly Tyr Val Tyr Thr Ala Cys Lys Cys Gly Leu Val Pro Val Leu Ala
           420                 425                 430

Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
       435                 440                 445

Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
   450                 455                 460

Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
465                 470                 475                 480

Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
                485                 490                 495

Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
           500                 505                 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
       515                 520                 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
   530                 535                 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
545                 550                 555                 560
```

```
Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
                565                 570                 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
            580                 585                 590

Leu Leu Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu Ala Arg Ser
        595                 600                 605

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
    610                 615                 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
625                 630                 635                 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
                645                 650                 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
            660                 665                 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
        675                 680                 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
    690                 695                 700

Ala Cys Glu Phe Leu Arg Lys
705                 710
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<210> 70
<211> 597
<212> DNA
<213> Homo sapiens

<400> 70
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aacttccagg acaaccaatt ccaggggaag tggtatgtgg taggcctggc agggaatgca 180
attctcagag aagacaaaga cccgcaaaag atgtatgcca ccatctatga gctgaaagaa 240
gacaagagct acaatgtcac ctccgtcctg tttaggaaaa agaagtgtga ctactggatc 300
aggacttttg ttccaggttg ccagcccggc gagttcacgc tgggcaacat taagagttac 360
cctggattaa cgagttacct cgtccgagtg gtgagcacca actacaacca gcatgctatg 420
gtgttcttca agaaagtttc tcaaaacagg gagtacttca agatcaccct ctacgggaga 480
accaaggagc tgacttcgga actaaaggag aacttcatcc gcttctccaa atatctgggc 540
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<210> 71
<211> 198
<212> PRT
<213> Homo sapiens

<400> 71
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Met Pro Leu Gly Leu Leu Trp Leu Gly Leu Ala Leu Leu Gly Ala Leu
  1               5                  10                  15
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His Ala Gln Ala Gln Asp Ser Thr Ser Asp Leu Ile Pro Ala Pro Pro
            20                  25                  30

Leu Ser Lys Val Pro Leu Gln Gln Asn Phe Gln Asp Asn Gln Phe Gln
        35                  40                  45

Gly Lys Trp Tyr Val Val Gly Leu Ala Gly Asn Ala Ile Leu Arg Glu
    50                  55                  60

Asp Lys Asp Pro Gln Lys Met Tyr Ala Thr Ile Tyr Glu Leu Lys Glu
65                  70                  75                  80

Asp Lys Ser Tyr Asn Val Thr Ser Val Leu Phe Arg Lys Lys Lys Cys
                85                  90                  95

Asp Tyr Trp Ile Arg Thr Phe Val Pro Gly Cys Gln Pro Gly Glu Phe
            100                 105                 110

Thr Leu Gly Asn Ile Lys Ser Tyr Pro Gly Leu Thr Ser Tyr Leu Val
        115                 120                 125

Arg Val Val Ser Thr Asn Tyr Asn Gln His Ala Met Val Phe Phe Lys
    130                 135                 140

Lys Val Ser Gln Asn Arg Glu Tyr Phe Lys Ile Thr Leu Tyr Gly Arg
145                 150                 155                 160

Thr Lys Glu Leu Thr Ser Glu Leu Lys Glu Asn Phe Ile Arg Phe Ser
                165                 170                 175

Lys Tyr Leu Gly Leu Pro Glu Asn His Ile Val Phe Pro Val Pro Ile
            180                 185                 190

Asp Gln Cys Ile Asp Gly
        195
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<210> 72
<211> 2334
<212> DNA
<213> Homo sapiens

<400> 72

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ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat 300
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ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct 480
caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga 540
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tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa 660
gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttcccctt 720
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<210> 73
<211> 2116
<212> DNA
<213> Homo sapiens

<400> 73
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gcagagcaat ggtggccagg ctggggctgg ggctgctgct gctggcactg ctcctaccca 120
cgcagattta ttccagtgaa acaacaactg gaacttcaag taactcctcc cagagtactt 180
ccaactctgg gttggcccca aatccaacta atgccaccac caaggcggct ggtggtgccc 240
tgcagtcaac agccagtctc ttcgtggtct cactctctct tctgcatctc tactcttaag 300
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gtctggaagt ccaatgtggc aaggaaaaac aggtcttcat cgaatctact aattccacac 420
cttttattga cacagaaaat gttgagaatc ccaaatttga ttgatttgaa gaacatgtga 480
gaggtttgac tagatgatga atgccaatat taaatctgct ggagtttcat gtacaagatg 540
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atggacactt aatactacct tgaaaataag aatagaaata aaggatggga ttgtggaatg 660
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ataaaaagaa acggtg 2116

<210> 74
<211> 80
<212> PRT
<213> Homo sapiens

<400> 74
Met Gly Arg Ala Met Val Ala Arg Leu Gly Leu Gly Leu Leu Leu Leu
1 5 10 15

Ala Leu Leu Leu Pro Thr Gln Ile Tyr Ser Ser Glu Thr Thr Thr Gly
20 25 30

Thr Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro
35 40 45

Asn Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser
50 55 60

Thr Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser
65 70 75 80

<210> 75
<211> 1864
<212> DNA
<213> Homo sapiens

<400> 75
gtggtttttc ggatcatgtc tggtggctcc gcggattata acagagaaca tggcggccca 60
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cttt 1864

<210> 76
<211> 407
<212> PRT
<213> Homo sapiens

<400> 76
Met Ser Gly Gly Ser Ala Asp Tyr Asn Arg Glu His Gly Gly Pro Glu
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Gly Met Asp Pro Asp Gly Val Ile Glu Ser Asn Trp Asn Glu Ile Val
20 25 30

Asp Asn Phe Asp Asp Met Asn Leu Lys Glu Ser Leu Leu Arg Gly Ile
35 40 45

Tyr Ala Tyr Gly Phe Glu Lys Pro Ser Ala Ile Gln Gln Arg Ala Ile
50 55 60

Ile Pro Cys Ile Lys Gly Tyr Asp Val Ile Ala Gln Ala Gln Ser Gly
65 70 75 80

Thr Gly Lys Thr Ala Thr Phe Ala Ile Ser Ile Leu Gln Gln Leu Glu
85 90 95

Ile Glu Phe Lys Glu Thr Gln Ala Leu Val Leu Ala Pro Thr Arg Glu
100 105 110

Leu Ala Gln Gln Ile Gln Lys Val Ile Leu Ala Leu Gly Asp Tyr Met
115 120 125

Gly Ala Thr Cys His Ala Cys Ile Gly Gly Thr Asn Val Arg Asn Glu
130 135 140

Met Gln Lys Leu Gln Ala Glu Ala Pro His Ile Val Val Gly Thr Pro
145 150 155 160

Gly Arg Val Phe Asp Met Leu Asn Arg Arg Tyr Leu Ser Pro Lys Trp
165 170 175

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Ile Lys Met Phe Val Leu Asp Glu Ala Asp Glu Met Leu Ser Arg Gly
            180                 185                 190

Phe Lys Asp Gln Ile Tyr Glu Ile Phe Gln Lys Leu Asn Thr Ser Ile
        195                 200                 205

Gln Val Val Phe Ala Ser Ala Thr Met Pro Thr Asp Val Leu Glu Val
    210                 215                 220

Thr Lys Lys Phe Met Arg Asp Pro Ile Arg Ile Leu Val Lys Lys Glu
225                 230                 235                 240

Glu Leu Thr Leu Glu Gly Ile Lys Gln Phe Tyr Ile Asn Val Glu Arg
                245                 250                 255

Glu Glu Trp Lys Leu Asp Thr Leu Cys Asp Leu Tyr Glu Thr Leu Thr
            260                 265                 270

Ile Thr Gln Ala Val Ile Phe Leu Asn Thr Arg Arg Lys Val Asp Trp
        275                 280                 285

Leu Thr Glu Lys Met His Ala Arg Asp Phe Thr Val Ser Ala Leu His
    290                 295                 300

Gly Asp Met Asp Gln Lys Glu Arg Asp Val Ile Met Arg Glu Phe Arg
305                 310                 315                 320

Ser Gly Ser Ser Arg Val Leu Ile Thr Thr Asp Leu Leu Ala Arg Gly
                325                 330                 335

Ile Asp Val Gln Gln Val Ser Leu Val Ile Asn Tyr Asp Leu Pro Thr
            340                 345                 350

Asn Arg Glu Asn Tyr Ile His Arg Ile Gly Arg Gly Gly Arg Phe Gly
        355                 360                 365

Arg Lys Gly Val Ala Ile Asn Phe Val Thr Glu Glu Asp Lys Arg Ile
    370                 375                 380

Leu Arg Asp Ile Glu Thr Phe Tyr Asn Thr Thr Val Glu Glu Met Pro
385                 390                 395                 400

Met Asn Val Ala Asp Leu Ile
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<210> 77
<211> 1670
<212> DNA
<213> Homo sapiens

<400> 77
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ggctcagggg actatgactc catgaaggaa ccctgtttcc gtgaagaaaa tgctaatttc 180
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gatgccgtgg caaactggta ctttgggaac ttcctatgca aggcagtcca tgtcatctac 420
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tgctggtttt tcagttttca ggagtgggtt gatttcagca cctacagtgt acagtcttgt 1620
attaagttgt taataaaagt acatgttaaa cttaaaaaaa aaaaaaaaaa 1670

<210> 78
<211> 352
<212> PRT
<213> Homo sapiens

<400> 78
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Gly Ser Gly Asp Tyr Asp Ser Met Lys Glu Pro Cys Phe Arg Glu Glu
20 25 30

Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
35 40 45

Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
50 55 60

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
65 70 75 80

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
85 90 95

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
100 105 110

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
115 120 125

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
130 135 140

```
Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val
145                 150                 155                 160

Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn
                165                 170                 175

Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn
            180                 185                 190

Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu
        195                 200                 205

Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser
    210                 215                 220

Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr
225                 230                 235                 240

Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr
                245                 250                 255

Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln
            260                 265                 270

Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu
        275                 280                 285

Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe
    290                 295                 300

Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val
305                 310                 315                 320

Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly
                325                 330                 335

His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser Phe His Ser Ser
            340                 345                 350
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<210> 79
<211> 1262
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (53)..(53)
<223> n is a, c, g, or t

<220>
<221> misc_feature
<222> (83)..(83)
<223> n is a, c, g, or t

<220>
<221> misc_feature

<222> (897)..(897)
<223> n is a, c, g, or t

<400> 79
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cagagccgct ggtagcctaa ggngggggggg cagccaggag aaagccccgc cgctgctcgt 120
cccgcccctc gggtgccagc accgcccctg ctgcggcggg tgaggggcgg ggcggggccg 180
cggcgtatat aaggctaggc ggggcgccgc tcttttgttt cttgctgcag caacgcgagt 240
gggagcacca ggatctcggg ctcggaacga gactgcacgg tgacgtgacg gccgggcggg 300
ggcccagggt gtggtcggat ccggtgcacc gcgggcgcgc aacccggaca ggcgcttctc 360
ggaccggacg caggggccgc gaccacgccc tgggaccgag aagaggggtg cggacgcgcc 420
cagatcctcg gccttggggc tgctcggcag ccttggcgcg agtgccacgt cgagaggcgt 480
cggcggggag cgcggaaggg gacggcctgc gcccaggccc aggtcaagcg ccttggtttg 540
cccactagga ttgttttaag aaaatggcag acaaaccaga catgggggaa atcgccagct 600
tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag 660
agagtgagtg tgcctcggtc tccgcgcccc agcccagccc ctcaccctgc tcttccttgc 720
aaacccactc ctccaccccc caccccgccg ttgtccccgg tgtgggcggc cccggcactc 780
tttcagtttc acaaagcgcc ttgtttctcc ccagccccaa gcttccttct aaatcccaca 840
cctcgtggtg ctcatcacac cgggaagcac ctcggttgcg ggtgggggggt tgcagcnccc 900
ctccagcgcc ccgttccgtc tcaagccatt gagcaggaga agcggagtga aatttcctaa 960
gatcctggag gatttcctac cccccgtctc tcggagcacc ccagtcgctg atgtggagaa 1020
gagccaccct gcaagatgga cacgagtcca caagctgcac tgtgaacctg cgagcccgcg 1080
ccgatgccac cggcctgtgg tcgtctgaag ggacccccccc ccaatcggac tgccaaattc 1140
tcggtttgcc ccgggatatt atagaaaatt atttgtatga ataatgaaaa taaaacacac 1200
ctcgttggca tggctggcgg tggtctgagt gttttagtta gtatgggtgc agtccactgc 1260
ag 1262

<210> 80
<211> 49
<212> PRT
<213> Homo sapiens

<400> 80
Asp Cys Phe Lys Lys Met Ala Asp Lys Pro Asp Met Gly Glu Ile Ala
1 5 10 15

Ser Phe Asp Lys Ala Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn
20 25 30

Thr Leu Pro Thr Lys Glu Thr Ile Glu Gln Glu Lys Arg Ser Glu Ile
35 40 45

Ser

<210> 81
<211> 1198
<212> DNA
<213> Homo sapiens

<400> 81
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agctgaggaa gctcttcatt ggagggttga gctttgaaac aactgatgag agcctgagga 120
gccatttga gcaatgggga acgctcacgg actgtgtggt aatgagagat ccaaacacca 180
agcgctctag gggctttggg tttgtcacat atgccactgt ggaggaggtg gatgcagcta 240
tgaatgcaag gccacacaag gtggatggaa gagttgtgga accaaagaga gctgtctcca 300

gagaagattc tcaaagacca ggtgcccact taactgtgaa aaagatattt gttggtggca 360
ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg 420
aagtgattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gcctttgtaa 480
cctttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtgaatg 540
gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca 600
gccaaagagg tcgaagtggt tctggaaact ttggtggtgg tcgtggaggt ggtttcggtg 660
ggaatgacaa cttcggtcgt ggaggaaact tcagtggtcg tggtggcttt ggtggcagcc 720
gtggtggtgg tggatatggt ggcagtgggg atggctataa tggatttggc aatgatggaa 780
gcaattttgg aggtggtgga agctacaatg attttgggaa ttacaacaat cagtcttcaa 840
attttggacc catgaaggga ggaaattttg gaggcagaag ctctggcccc tatggcggtg 900
gaggccaata ctttgcaaaa ccacgaaacc aaggtggcta tggcggttcc agcagcagca 960
gtagctatgg cagtggcaga agattttaat tagggaggag tctgctacta gtcttatcag 1020
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acctttatct gagccactgt acttcgttat cacgccatgc agtttacatg agctgttctg 1140
cagctcgaaa ttccattttg tgaatgggtt ttttttttta ataaactgta tttaacttt 1198

<210> 82
<211> 320
<212> PRT
<213> Homo sapiens

<400> 82
Met Ser Lys Ser Glu Ser Pro Lys Glu Pro Glu Gln Leu Arg Lys Leu
1 5 10 15

Phe Ile Gly Gly Leu Ser Phe Glu Thr Thr Asp Glu Ser Leu Arg Ser
20 25 30

His Phe Glu Gln Trp Gly Thr Leu Thr Asp Cys Val Val Met Arg Asp
35 40 45

Pro Asn Thr Lys Arg Ser Arg Gly Phe Gly Phe Val Thr Tyr Ala Thr
50 55 60

Val Glu Glu Val Asp Ala Ala Met Asn Ala Arg Pro His Lys Val Asp
65 70 75 80

Gly Arg Val Val Glu Pro Lys Arg Ala Val Ser Arg Glu Asp Ser Gln
85 90 95

Arg Pro Gly Ala His Leu Thr Val Lys Lys Ile Phe Val Gly Gly Ile
100 105 110

Lys Glu Asp Thr Glu Glu His His Leu Arg Asp Tyr Phe Glu Gln Tyr
115 120 125

Gly Lys Ile Glu Val Ile Glu Ile Met Thr Asp Arg Gly Ser Gly Lys
130 135 140

Lys Arg Gly Phe Ala Phe Val Thr Phe Asp Asp His Asp Ser Val Asp
145 150 155 160

Lys Ile Val Ile Gln Lys Tyr His Thr Val Asn Gly His Asn Cys Glu
165 170 175

Val Arg Lys Ala Leu Ser Lys Gln Glu Met Ala Ser Ala Ser Ser Ser
180 185 190

```
Gln Arg Gly Arg Ser Gly Ser Gly Asn Phe Gly Gly Gly Arg Gly Gly
        195                 200                 205

Gly Phe Gly Gly Asn Asp Asn Phe Gly Arg Gly Gly Asn Phe Ser Gly
    210                 215                 220

Arg Gly Gly Phe Gly Gly Ser Arg Gly Gly Gly Gly Tyr Gly Gly Ser
225                 230                 235                 240

Gly Asp Gly Tyr Asn Gly Phe Gly Asn Asp Gly Ser Asn Phe Gly Gly
                245                 250                 255

Gly Gly Ser Tyr Asn Asp Phe Gly Asn Tyr Asn Asn Gln Ser Ser Asn
            260                 265                 270

Phe Gly Pro Met Lys Gly Gly Asn Phe Gly Gly Arg Ser Ser Gly Pro
        275                 280                 285

Tyr Gly Gly Gly Gly Gln Tyr Phe Ala Lys Pro Arg Asn Gln Gly Gly
    290                 295                 300

Tyr Gly Gly Ser Ser Ser Ser Ser Ser Tyr Gly Ser Gly Arg Arg Phe
305                 310                 315                 320
```

<210> 83
<211> 1125
<212> DNA
<213> Homo sapiens

<400> 83
gtctccccca ctgtcagcac ctcttctgtg tggtgagtgg accgcttacc ccactaggtg 60
aagatgtcag cccaggagag ctgcctcagc ctcatcaagt acttcctctt cgttttcaac 120
ctcttcttct tcgtcctcgg cagcctgatc ttctgcttcg gcatctggat cctcatcgac 180
aagaccagct tcgtgtcctt tgtgggcttg gccttcgtgc ctctgcagat ctggtccaaa 240
gtcctggcca tctcaggaat cttcaccatg ggcatcgccc tcctgggttg tgtgggggcc 300
ctcaaggagc tccgctgcct cctgggcctg tattttggga tgctgctgct cctgtttgcc 360
acacagatca ccctgggaat cctcatctcc actcagcggg cccagctgga gcgaagcttg 420
cgggacgtcg tagagaaaac catccaaaag tacggcacca accccgagga gaccgcggcc 480
gaggagagct gggactatgt gcagttccag ctgcgctgct gcggctggca ctacccgcag 540
gactggttcc aagtcctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc 600
tcctgctaca acttgtcggc gaccaacgac tccacaatcc tagataaggt gatcttgccc 660
cagctcagca ggcttggaca cctggcgcgg tccagacaca gtgcagacat ctgcgctgtc 720
cctgcagaga gccacatcta ccgcgagggc tgcgcgcagg gcctccagaa gtggctgcac 780
aacaacctta tttccatagt gggcatttgc ctgggcgtcg gcctactcga gctcgggttc 840
atgacgctct cgatattcct gtgcagaaac ctggaccacg tctacaaccg gctcgctcga 900
taccgttagg ccccgccctc cccaaagtcc cgccccgccc ccgtcacgtg cgctgggcac 960
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cattcccctg gggacccacg tggctgcgtg cccctgctgc tgtcacctct cccacgggac 1080
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<210> 84
<211> 281

<212> PRT
<213> Homo sapiens

<400> 84

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Met Ser Ala Gln Glu Ser Cys Leu Ser Leu Ile Lys Tyr Phe Leu Phe
  1               5                  10                  15

Val Phe Asn Leu Phe Phe Phe Val Leu Gly Ser Leu Ile Phe Cys Phe
             20                  25                  30

Gly Ile Trp Ile Leu Ile Asp Lys Thr Ser Phe Val Ser Phe Val Gly
         35                  40                  45

Leu Ala Phe Val Pro Leu Gln Ile Trp Ser Lys Val Leu Ala Ile Ser
     50                  55                  60

Gly Ile Phe Thr Met Gly Ile Ala Leu Leu Gly Cys Val Gly Ala Leu
 65                  70                  75                  80

Lys Glu Leu Arg Cys Leu Leu Gly Leu Tyr Phe Gly Met Leu Leu Leu
                 85                  90                  95

Leu Phe Ala Thr Gln Ile Thr Leu Gly Ile Leu Ile Ser Thr Gln Arg
            100                 105                 110

Ala Gln Leu Glu Arg Ser Leu Arg Asp Val Val Glu Lys Thr Ile Gln
        115                 120                 125

Lys Tyr Gly Thr Asn Pro Glu Glu Thr Ala Ala Glu Glu Ser Trp Asp
    130                 135                 140

Tyr Val Gln Phe Gln Leu Arg Cys Cys Gly Trp His Tyr Pro Gln Asp
145                 150                 155                 160

Trp Phe Gln Val Leu Ile Leu Arg Gly Asn Gly Ser Glu Ala His Arg
                165                 170                 175

Val Pro Cys Ser Cys Tyr Asn Leu Ser Ala Thr Asn Asp Ser Thr Ile
            180                 185                 190

Leu Asp Lys Val Ile Leu Pro Gln Leu Ser Arg Leu Gly His Leu Ala
        195                 200                 205

Arg Ser Arg His Ser Ala Asp Ile Cys Ala Val Pro Ala Glu Ser His
    210                 215                 220

Ile Tyr Arg Glu Gly Cys Ala Gln Gly Leu Gln Lys Trp Leu His Asn
225                 230                 235                 240

Asn Leu Ile Ser Ile Val Gly Ile Cys Leu Gly Val Gly Leu Leu Glu
                245                 250                 255

Leu Gly Phe Met Thr Leu Ser Ile Phe Leu Cys Arg Asn Leu Asp His
            260                 265                 270

Val Tyr Asn Arg Leu Ala Arg Tyr Arg
        275                 280
```

<210> 85
<211> 1216
<212> DNA
<213> Homo sapiens

<400> 85
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ggtgctgagc tccccactgg ctttggctgg ggacacccga ccatgtttct tgcagcagga 180
taagtatgag tgtcatttct tcaacgggac ggagcgggtg cggttcctgc acagaggcat 240
ctataaccaa caggagaacg tgcgcttcga cagcgacgtg ggggagtacc gggcggtgac 300
ggagctgggg cggcctgacg ctgagtactg gaacagccag aaggacatcc tggagcaggc 360
gcgggccgcg gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt 420
gcagcggcga gttgagccta aggtgactgt gtatcctgca aggacccaga ccctgcagca 480
ccacaacctc ctggtctgct ctgtgaatgg tttctatcca ggcagcattg aagtcaggtg 540
gttccggaac ggccaggaag agaaggctgg ggtggtgtcc acaggcctga ttcagaatgg 600
agactggacc ttccagattc tggtgatgct ggaaacagtt cctcggagtg gagaggttta 660
cacctgccaa gtggagcacc caagcgtgac gagccctctc acagtggaat ggagagcaca 720
gtctgaatct gcacagagca agatgctgag tggaatcggg ggctttgtgc tgggcctgct 780
cttccttggg gccgggctat tcatctactt caagaatcag aaagggcact ctggacttca 840
cccaacagga ctcgtgagct gaagtgcaga tgaccacatt caaggggaa ccttctgccc 900
cagctttgca tgatgaaaag ctttcctgct tggctcttat tcttccacaa gagaggactt 960
tctcaggccc tggttgctac cggttcagca actctgcaga aaatgtccat ccttgtggct 1020
tcctcagctc ctgcccttgg cctgaagtcc cagcattgat ggcagtgcct catcttcaac 1080
tttagtgctc ccctttacct aaccctacgg cctcccatgc atctgtactc cccctgtgcc 1140
acaaatggac tacgttatta aatttttctg aagcccagag ttaaaaatca tctgtccacc 1200
tggcaccaaa gacaaa 1216

<210> 86
<211> 266
<212> PRT
<213> Homo sapiens

<400> 86
Met Val Cys Leu Lys Leu Pro Gly Gly Ser Tyr Met Ala Val Leu Thr
1 5 10 15

Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu Ala Gly Asp Thr
20 25 30

Arg Pro Cys Phe Leu Gln Gln Asp Lys Tyr Glu Cys His Phe Phe Asn
35 40 45

Gly Thr Glu Arg Val Arg Phe Leu His Arg Gly Ile Tyr Asn Gln Gln
50 55 60

Glu Asn Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr
65 70 75 80

Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile
85 90 95

Leu Glu Gln Ala Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr
100 105 110

```
Gly Ala Val Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val
        115                 120                 125

Thr Val Tyr Pro Ala Arg Thr Gln Thr Leu Gln His His Asn Leu Leu
    130                 135                 140

Val Cys Ser Val Asn Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp
145                 150                 155                 160

Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu
                165                 170                 175

Ile Gln Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Thr
            180                 185                 190

Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser
        195                 200                 205

Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Gln Ser Glu Ser Ala
    210                 215                 220

Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu Gly Leu Leu
225                 230                 235                 240

Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Lys Asn Gln Lys Gly His
                245                 250                 255

Ser Gly Leu His Pro Thr Gly Leu Val Ser
            260                 265
```

<210> 87
<211> 1881
<212> DNA
<213> Homo sapiens

<400> 87

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gaattcggca cgagctaacg cggtccccgg cacgcaccat ctgttgccat cccggccggc 60
cgaggccatt gcagattttg gaagatggca aagttcatga cacccgtgat ccaggacaac 120
ccctcaggct ggggtccctg tgcggttccc gagcagtttc gggatatgcc ctaccagccg 180
ttcagcaaag gagatcggct aggaaaggtt gcagactgga caggagccac ataccaagat 240
aagaggtaca caaataagta ctcctctcag tttggtggtg gaagtcaata tgcttatttc 300
catgaggagg atgaaagtag cttccagctg gtggatacag cgcgcacaca gaagacggcc 360
taccagcgga atcgaatgag atttgcccag aggaacctcc gcagagacaa agatcgtcgg 420
aacatgttgc agttcaacct gcagatcctg cctaagagtg ccaaacagaa agagagagaa 480
cgcattcgac tgcagaaaaa gttccagaaa caatttgggg ttaggcagaa atgggatcag 540
aaatcacaga aaccccgaga ctcttcagtt gaagttcgta gtgattggga agtgaaagag 600
gaaatggatt ttcctcagtt gatgaagatg cgctacttgg aagtatcaga gccacaggac 660
attgagtgtt gtggggccct agaatactac gacaaagcct ttgaccgcat caccacgagg 720
agtgagaagc cactgcggag catcaagcgc atcttccaca ctgtcaccac cacagacgac 780
cctgtcatcc gcaagctggc aaaaactcag gggaatgtgt ttgccactga tgccatcctg 840
gccacgctga tgagctgtac ccgctcagtg tattcctggg atattgtcgt ccagagagtt 900
gggtccaaac tcttctttga caagagagac aactctgact ttgacctcct gacagtgagt 960
gagactgcca atgagccccc tcaagatgaa ggtaattcct tcaattcacc ccgcaacctg 1020
gccatggagg caacctacat caaccacaat ttctcccagc agtgcttgag aatggggaag 1080
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 1140
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 1200
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 1260
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atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 1320
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gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 1440
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cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgggg cattttacgc 1560
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tttaaaaaaa aaaaaaaaaa a 1881

<210> 88
<211> 548
<212> PRT
<213> Homo sapiens

<400> 88
Met Ala Lys Phe Met Thr Pro Val Ile Gln Asp Asn Pro Ser Gly Trp
1 5 10 15

Gly Pro Cys Ala Val Pro Glu Gln Phe Arg Asp Met Pro Tyr Gln Pro
20 25 30

Phe Ser Lys Gly Asp Arg Leu Gly Lys Val Ala Asp Trp Thr Gly Ala
35 40 45

Thr Tyr Gln Asp Lys Arg Tyr Thr Asn Lys Tyr Ser Ser Gln Phe Gly
50 55 60

Gly Gly Ser Gln Tyr Ala Tyr Phe His Glu Glu Asp Glu Ser Ser Phe
65 70 75 80

Gln Leu Val Asp Thr Ala Arg Thr Gln Lys Thr Ala Tyr Gln Arg Asn
85 90 95

Arg Met Arg Phe Ala Gln Arg Asn Leu Arg Arg Asp Lys Asp Arg Arg
100 105 110

Asn Met Leu Gln Phe Asn Leu Gln Ile Leu Pro Lys Ser Ala Lys Gln
115 120 125

Lys Glu Arg Glu Arg Ile Arg Leu Gln Lys Lys Phe Gln Lys Gln Phe
130 135 140

Gly Val Arg Gln Lys Trp Asp Gln Lys Ser Gln Lys Pro Arg Asp Ser
145 150 155 160

Ser Val Glu Val Arg Ser Asp Trp Glu Val Lys Glu Glu Met Asp Phe
165 170 175

Pro Gln Leu Met Lys Met Arg Tyr Leu Glu Val Ser Glu Pro Gln Asp
180 185 190

Ile Glu Cys Cys Gly Ala Leu Glu Tyr Tyr Asp Lys Ala Phe Asp Arg
195 200 205

```
Ile Thr Thr Arg Ser Glu Lys Pro Leu Arg Ser Ile Lys Arg Ile Phe
    210                 215                 220

His Thr Val Thr Thr Thr Asp Asp Pro Val Ile Arg Lys Leu Ala Lys
225                 230                 235                 240

Thr Gln Gly Asn Val Phe Ala Thr Asp Ala Ile Leu Ala Thr Leu Met
                245                 250                 255

Ser Cys Thr Arg Ser Val Tyr Ser Trp Asp Ile Val Val Gln Arg Val
            260                 265                 270

Gly Ser Lys Leu Phe Phe Asp Lys Arg Asp Asn Ser Asp Phe Asp Leu
        275                 280                 285

Leu Thr Val Ser Glu Thr Ala Asn Glu Pro Pro Gln Asp Glu Gly Asn
    290                 295                 300

Ser Phe Asn Ser Pro Arg Asn Leu Ala Met Glu Ala Thr Tyr Ile Asn
305                 310                 315                 320

His Asn Phe Ser Gln Gln Cys Leu Arg Met Gly Lys Glu Arg Tyr Asn
                325                 330                 335

Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met Asp Lys Asn Glu
            340                 345                 350

Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys Leu Gly Asp Asp
        355                 360                 365

Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val Met Thr Gly Ala
    370                 375                 380

Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu Asn Glu Trp Asp
385                 390                 395                 400

Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys Leu Asp Ser Gln
                405                 410                 415

Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn Ser Tyr Lys Leu
            420                 425                 430

Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser Glu Tyr Leu Lys
        435                 440                 445

Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser Ser Arg His Val
    450                 455                 460

Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe Ala Ser Gln Ile
465                 470                 475                 480

Asn Leu Ser Val Glu Asn Ala Trp Gly Ile Leu Arg Cys Val Ile Asp
                485                 490                 495

Ile Cys Met Lys Leu Glu Glu Gly Lys Tyr Leu Ile Leu Lys Asp Pro
            500                 505                 510
```

```
Asn Lys Gln Val Ile Arg Val Tyr Ser Leu Pro Asp Gly Thr Phe Ser
        515                 520                 525

Ser Asp Glu Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
    530                 535                 540

Glu Glu Glu Thr
545
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<210> 89
<211> 670
<212> DNA
<213> Homo sapiens

<400> 89
cggccacgag gcggaatccc ttctgctctc ccagcgcagc gccgccgccc ggcccctcca 60
gcttcccgga ccatggccaa cctggagcgc accttcatcg ccatcaagcc ggacggcgtg 120
cagcgcggcc tggtgggcga gatcatcaag cgcttcgagc agaagggatt ccgcctcgtg 180
gccatgaagt tcctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa 240
gaccgaccat tcttccctgg gctggtgaag tacatgaact cagggccggt tgtggccatg 300
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gcagattcaa agccaggcac cattcgtggg gacttctgca ttcaggttgg caggaacatc 420
attcatggca gtgattcagt aaaaagtgct gaaaaagaaa tcagcctatg gtttaagcct 480
gaagaactgg ttgactacaa gtcttgtgct catgactggg tctatgaata agaggtggac 540
acaacagcag tctccttcag cacggcgtgg tgtgtccctg gacacagctc ttcattccat 600
tgacttagag gcaacaggat tgatcattct tttatagagc atatttgcca ataaagcttt 660
tggaagccgg 670

<210> 90
<211> 152
<212> PRT
<213> Homo sapiens

<400> 90
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Met Ala Asn Leu Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val
  1               5                  10                  15

Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly
             20                  25                  30

Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu
         35                  40                  45

Lys Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu
     50                  55                  60

Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly
 65                  70                  75                  80

Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro
                 85                  90                  95

Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val
            100                 105                 110
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<211> 312
<212> PRT
<213> Homo sapiens

<400> 97
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20 25 30

Ser Val Lys Ile Glu Cys Arg Ser Leu Asp Phe Gln Ala Thr Thr Met
35 40 45

Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr
50 55 60

```
Ser Asn Glu Gly Ser Lys Ala Thr Tyr Glu Gln Gly Val Glu Lys Asp
 65                  70                  75                  80

Lys Phe Leu Ile Asn His Ala Ser Leu Thr Leu Ser Thr Leu Thr Val
                 85                  90                  95

Thr Ser Ala His Pro Glu Asp Ser Ser Phe Tyr Ile Cys Ser Ala Arg
            100                 105                 110

Glu Ser Thr Ser Asp Pro Lys Asn Glu Gln Phe Phe Gly Pro Gly Thr
        115                 120                 125

Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val
    130                 135                 140

Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala
145                 150                 155                 160

Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu
                165                 170                 175

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp
            180                 185                 190

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
        195                 200                 205

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
    210                 215                 220

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
225                 230                 235                 240

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
                245                 250                 255

Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln
            260                 265                 270

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
        275                 280                 285

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
    290                 295                 300

Val Lys Arg Lys Asp Ser Arg Gly
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<210> 98
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<212> DNA
<213> Homo sapiens

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tgctgctcac atctgtggtc cagggcaggg ccactccaga gaattacgtg taccagggac 180

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<210> 99
<211> 258
<212> PRT
<213> Homo sapiens

<400> 99

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Ala Leu Leu Met Val Leu Leu Thr Ser Val Val Gln Gly Arg Ala Thr
             20                  25                  30

Pro Glu Asn Tyr Val Tyr Gln Gly Arg Gln Glu Cys Tyr Ala Phe Asn
         35                  40                  45

Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
     50                  55                  60

Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
 65                  70                  75                  80

Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
                 85                  90                  95

Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
            100                 105                 110

Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
        115                 120                 125

Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
    130                 135                 140
```

```
His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
145                 150                 155                 160

Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg
                165                 170                 175

Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
            180                 185                 190

Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp
        195                 200                 205

Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser
    210                 215                 220

Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys
225                 230                 235                 240

Gly Val Gly Ile Phe Met His Arg Arg Ser Lys Lys Val Gln Arg Gly
                245                 250                 255

Ser Ala
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<210> 100
<211> 5022
<212> DNA
<213> Homo sapiens

<400> 100

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<210> 101
<211> 1356
<212> PRT
<213> Homo sapiens

<400> 101

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Leu Ser Thr Arg Lys Ala Leu Ser Val Leu Lys Glu Gln Leu Glu Ala
             20                  25                  30

Val Leu Glu Gly His Leu Arg Glu Arg Lys Lys Cys Leu Thr Trp Lys
         35                  40                  45

Glu Val Trp Arg Ser Ser Phe Leu His His Ser Asn Arg Cys Ser Cys
     50                  55                  60

Phe His Trp Pro Gly Ala Ser Leu Met Leu Leu Ala Val Leu Leu Leu
 65                  70                  75                  80

Leu Gly Cys Cys Gly Gly Gln Pro Ala Gly Ser Arg Gly Val Gly Leu
                 85                  90                  95

Val Asn Ala Ser Ala Leu Phe Leu Leu Leu Leu Leu Asn Leu Val Leu
            100                 105                 110

Ile Gly Arg Gln Asp Arg Leu Lys Arg Arg Glu Val Glu Arg Arg Leu
        115                 120                 125

Arg Gly Ile Ile Asp Gln Ile Gln Asp Ala Leu Arg Asp Gly Arg Glu
    130                 135                 140

Ile Gln Trp Pro Ser Ala Met Tyr Pro Asp Leu His Met Pro Phe Ala
145                 150                 155                 160

Pro Ser Trp Ser Leu His Trp Ala Tyr Arg Asp Gly His Leu Val Asn
                165                 170                 175

Leu Pro Val Ser Leu Leu Val Glu Gly Asp Ile Ile Ala Leu Arg Pro
            180                 185                 190

Gly Gln Glu Ser Phe Ala Ser Leu Arg Gly Ile Lys Asp Asp Glu His
        195                 200                 205

Ile Val Leu Glu Pro Gly Asp Leu Phe Pro Pro Phe Ser Pro Pro Pro
    210                 215                 220

Ser Pro Arg Gly Glu Val Glu Arg Gly Pro Gln Ser Pro Gln Gln His
225                 230                 235                 240

Arg Leu Phe Arg Val Leu Glu Thr Pro Val Ile Asp Asn Ile Arg Trp
                245                 250                 255

Cys Leu Asp Met Ala Leu Ser Arg Pro Val Thr Ala Leu Asp Asn Glu
            260                 265                 270
```

```
Arg Phe Thr Val Gln Ser Val Met Leu His Tyr Ala Val Pro Val Val
        275                 280                 285

Leu Ala Gly Phe Leu Ile Thr Asn Ala Leu Arg Phe Ile Phe Ser Ala
    290                 295                 300

Pro Gly Val Thr Ser Trp Gln Tyr Thr Leu Leu Gln Leu Gln Val Asn
305                 310                 315                 320

Gly Val Leu Pro Ile Leu Pro Leu Leu Phe Pro Val Leu Trp Val Leu
                325                 330                 335

Ala Thr Ala Cys Gly Glu Ala Arg Val Leu Ala Gln Met Ser Lys Ala
            340                 345                 350

Ser Pro Ser Ser Leu Leu Ala Lys Phe Ser Glu Asp Thr Leu Ser Ser
        355                 360                 365

Tyr Thr Glu Ala Val Ser Ser Gln Glu Met Leu Arg Cys Ile Trp Gly
    370                 375                 380

His Phe Leu Arg Val Leu Gly Gly Thr Ser Pro Thr Leu Ser His Ser
385                 390                 395                 400

Ser Ser Leu Leu His Ser Leu Gly Ser Val Thr Val Leu Cys Cys Val
                405                 410                 415

Asp Lys Gln Gly Ile Leu Ser Trp Pro Asn Pro Ser Pro Glu Thr Val
            420                 425                 430

Leu Phe Phe Ser Gly Lys Val Glu Pro Pro His Ser Ser His Glu Asp
        435                 440                 445

Leu Thr Asp Gly Leu Ser Thr Arg Ser Phe Cys His Pro Glu Pro His
    450                 455                 460

Glu Arg Asp Ala Leu Leu Ala Gly Ser Leu Asn Asn Thr Leu His Leu
465                 470                 475                 480

Ser Asn Glu Gln Glu Arg Gly Asp Trp Pro Gly Glu Ala Pro Lys Pro
                485                 490                 495

Pro Glu Pro Tyr Ser His His Lys Ala His Gly Arg Ser Lys His Pro
            500                 505                 510

Ser Gly Ser Asn Val Ser Phe Ser Arg Asp Thr Glu Gly Gly Glu Glu
        515                 520                 525

Glu Pro Ser Lys Thr Gln Pro Gly Met Glu Ser Asp Pro Tyr Glu Ala
    530                 535                 540

Glu Asp Phe Val Cys Asp Tyr His Leu Glu Met Leu Ser Leu Ser Gln
545                 550                 555                 560

Asp Gln Gln Asn Pro Ser Cys Ile Gln Phe Asp Asp Ser Asn Trp Gln
                565                 570                 575
```

Leu His Leu Thr Ser Leu Lys Pro Leu Gly Leu Asn Val Leu Leu Asn
580 585 590

Leu Cys Asp Ala Ser Val Thr Glu Arg Leu Cys Arg Phe Ser Asp His
595 600 605

Leu Cys Asn Ile Ala Leu Gln Glu Ser His Ser Ala Val Leu Pro Val
610 615 620

His Val Pro Trp Gly Leu Cys Glu Leu Ala Arg Leu Ile Gly Phe Thr
625 630 635 640

Pro Gly Ala Lys Glu Leu Phe Lys Gln Glu Asn His Leu Ala Leu Tyr
645 650 655

Arg Leu Pro Ser Ala Glu Thr Met Lys Glu Thr Ser Leu Gly Arg Leu
660 665 670

Ser Cys Val Thr Lys Arg Arg Pro Pro Leu Ser His Met Ile Ser Leu
675 680 685

Phe Ile Lys Asp Thr Thr Thr Ser Thr Glu Gln Met Leu Ser His Gly
690 695 700

Thr Ala Asp Val Val Leu Glu Ala Cys Thr Asp Phe Trp Asp Gly Ala
705 710 715 720

Asp Ile Tyr Pro Leu Ser Gly Ser Asp Arg Lys Lys Val Leu Asp Phe
725 730 735

Tyr Gln Arg Ala Cys Leu Ser Gly Tyr Cys Ser Ala Phe Ala Tyr Lys
740 745 750

Pro Met Asn Cys Ala Leu Ser Ser Gln Leu Asn Gly Lys Cys Ile Glu
755 760 765

Leu Val Gln Val Pro Gly Gln Ser Ser Ile Phe Thr Met Cys Glu Leu
770 775 780

Pro Ser Thr Ile Pro Ile Lys Gln Asn Ala Arg Arg Ser Ser Trp Ser
785 790 795 800

Ser Asp Glu Gly Ile Gly Glu Val Leu Glu Lys Glu Asp Cys Met Gln
805 810 815

Ala Leu Ser Gly Gln Ile Phe Met Gly Met Val Ser Ser Gln Tyr Gln
820 825 830

Ala Arg Leu Asp Ile Val Arg Leu Ile Asp Gly Leu Val Asn Ala Cys
835 840 845

Ile Arg Phe Val Tyr Phe Ser Leu Glu Asp Glu Leu Lys Ser Lys Val
850 855 860

Phe Ala Glu Lys Met Gly Leu Glu Thr Gly Trp Asn Cys His Ile Ser
865 870 875 880

```
Leu Thr Pro Asn Gly Asp Met Pro Gly Ser Glu Ile Pro Pro Ser Ser
                885                 890                 895

Pro Ser His Ala Gly Ser Leu His Asp Asp Leu Asn Gln Val Ser Arg
            900                 905                 910

Asp Asp Ala Glu Gly Leu Leu Leu Met Glu Glu Glu Gly His Ser Asp
        915                 920                 925

Leu Ile Ser Phe Gln Pro Thr Asp Ser Asp Ile Pro Ser Phe Leu Glu
    930                 935                 940

Asp Ser Asn Arg Ala Lys Leu Pro Arg Gly Ile His Gln Val Arg Pro
945                 950                 955                 960

His Leu Gln Asn Ile Asp Asn Val Pro Leu Leu Val Pro Leu Phe Thr
                965                 970                 975

Asp Cys Thr Pro Glu Thr Met Cys Glu Met Ile Lys Ile Met Gln Glu
            980                 985                 990

Tyr Gly Glu Val Thr Cys Cys Leu Gly Ser Ser Ala Asn Leu Arg Asn
        995                1000                1005

Ser Cys Leu Phe Leu Gln Ser Asp Ile Ser Ile Ala Leu Asp Pro Leu
   1010                1015                1020

Tyr Pro Ser Arg Cys Ser Trp Glu Thr Phe Gly Tyr Ala Thr Ser Ile
1025                1030                1035                1040

Ser Met Ala Gln Ala Ser Asp Gly Leu Ser Pro Leu Gln Leu Ser Gly
               1045                1050                1055

Gln Leu Asn Ser Leu Pro Cys Ser Leu Thr Phe Arg Gln Glu Glu Thr
           1060                1065                1070

Ile Ser Ile Ile Arg Leu Ile Glu Gln Ala Arg His Ala Thr Tyr Gly
       1075                1080                1085

Ile Arg Lys Cys Phe Leu Phe Leu Leu Gln Cys Gln Leu Thr Leu Val
   1090                1095                1100

Val Ile Gln Phe Leu Ser Cys Leu Val Gln Leu Pro Pro Leu Leu Ser
1105                1110                1115                1120

Thr Thr Asp Ile Leu Trp Leu Ser Cys Phe Cys Tyr Pro Leu Leu Ser
               1125                1130                1135

Ile Ser Leu Leu Gly Lys Pro Pro His Ser Ser Ile Met Ser Met Ala
           1140                1145                1150

Thr Gly Lys Asn Leu Gln Ser Ile Pro Lys Lys Thr Gln His Tyr Phe
       1155                1160                1165

Leu Leu Cys Phe Leu Leu Lys Phe Ser Leu Thr Ile Ser Ser Cys Leu
   1170                1175                1180
```

```
Ile Cys Phe Gly Phe Thr Leu Gln Ser Phe Cys Asp Ser Ser Arg Asp
1185                1190                1195                1200

Arg Asn Leu Thr Asn Cys Ser Ser Val Met Leu Pro Ser Asn Asp Asp
                1205                1210                1215

Arg Ala Pro Ala Trp Phe Glu Asp Phe Ala Asn Gly Leu Leu Ser Ala
            1220                1225                1230

Gln Lys Leu Thr Ala Ala Leu Ile Val Leu His Thr Val Phe Ile Ser
        1235                1240                1245

Ile Thr His Val His Arg Thr Lys Pro Leu Trp Arg Lys Ser Pro Leu
    1250                1255                1260

Thr Asn Leu Trp Trp Ala Val Thr Val Pro Val Val Leu Leu Gly Gln
1265                1270                1275                1280

Val Val Gln Thr Ala Val Asp Leu Gln Leu Trp Thr His Arg Asp Ser
                1285                1290                1295

His Val His Phe Gly Leu Glu Asp Val Pro Leu Leu Thr Trp Leu Leu
            1300                1305                1310

Gly Cys Leu Ser Leu Val Leu Val Val Val Thr Asn Glu Ile Val Lys
        1315                1320                1325

Leu His Glu Ile Arg Val Arg Val Arg Tyr Gln Lys Arg Gln Lys Leu
    1330                1335                1340

Gln Phe Glu Thr Lys Leu Gly Met Asn Ser Pro Phe
1345                1350                1355
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<210> 102
<211> 2030
<212> DNA
<213> Homo sapiens

<400> 102

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catgattgag atggccatcc tgcggttccc ttacgagtcc tgggggaccc cgttccagca 1080
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<210> 103
<211> 318
<212> PRT
<213> Homo sapiens

<400> 103
Met Ser Lys Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp
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Ser Arg Thr Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala
20 25 30

Asp Asp Leu Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val
35 40 45

Val Glu Lys Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys
50 55 60

Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met
65 70 75 80

Asp Leu Asp Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr
85 90 95

Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu
100 105 110

Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys
115 120 125

Asn Met Thr Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile
130 135 140

Val Arg Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile His Arg
145 150 155 160

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys Glu Gly His Val Lys
165 170 175

Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys
180 185 190

Thr Met Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn
195 200 205

Pro Glu Leu Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser
210 215 220

Leu Gly Ile Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu
225 230 235 240

Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro
245 250 255

Ser Pro Gln Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe
260 265 270

Thr Ala Gln Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu
275 280 285

Glu Leu Met Glu His Pro Phe Phe Thr Leu His Lys Thr Lys Lys Thr
290 295 300

Asp Ile Ala Ala Phe Val Lys Lys Ile Leu Gly Glu Asp Ser
305 310 315

<210> 104
<211> 1648
<212> DNA
<213> Homo sapiens

<400> 104
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gacttgcagc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg 180
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tgcatcgaca acgaggcgct ctacgacatc tgcttccgca ccctcaagct ggccacgccc 660
acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cacctccttg 720
cgcttcccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc 780
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aataaatcta ttgctgtcag ataccctt 1648

<210> 105
<211> 450
<212> PRT
<213> Homo sapiens

<400> 105
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Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
20 25 30

Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
35 40 45

Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
50 55 60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
65 70 75 80

Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
85 90 95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
100 105 110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
115 120 125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
130 135 140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
145 150 155 160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
165 170 175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
180 185 190

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
195 200 205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
210 215 220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
225 230 235 240

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Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
                245                 250                 255

Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
            260                 265                 270

Leu Thr Arg Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
        275                 280                 285

Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
    290                 295                 300

Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Arg
305                 310                 315                 320

Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Ser Lys
                325                 330                 335

Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
            340                 345                 350

Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ser Thr Phe Ile
        355                 360                 365

Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
    370                 375                 380

Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
385                 390                 395                 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
                405                 410                 415

Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
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Glu Gly Glu Met Tyr Glu Asp Asp Glu Glu Glu Ser Glu Ala Gln Gly
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Pro Lys
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<210> 106
<211> 1633
<212> DNA
<213> Homo sapiens

<400> 106

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catttaaaag gtagaacagg atcgacaaac aaggatttat gtcaggatct ctcagcctct 180
gtgttaccga gggcatttct aacagtcttc ttactacggc ctccgccgac cgcgcgctcg 240
ccccgccgct cctgctgcag ccccagggcc cctcgccgcc gccaccatgg acgccatcaa 300
gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc 360
ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg agctggtgtc 420
actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa 480
agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt 540
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aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga 720
gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaaat atgaagaggt 780
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atcccgcatg cct 1633

<210> 107
<211> 284
<212> PRT
<213> Homo sapiens

<400> 107
Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
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Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
20 25 30

Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
35 40 45

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
50 55 60

Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65 70 75 80

Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
85 90 95

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
100 105 110

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
115 120 125

Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
130 135 140

Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145 150 155 160

Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
165 170 175

Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Gln Val Arg Gln
180 185 190

Leu Glu Glu Gln Leu Arg Ile Met Asp Gln Thr Leu Lys Ala Leu Met
195 200 205

Ala Ala Glu Asp Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
210 215 220

Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225 230 235 240

Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
245 250 255

Glu Glu Lys Val Ala His Ala Lys Glu Glu Asn Leu Ser Met His Gln
260 265 270

Met Leu Asp Gln Thr Leu Leu Glu Leu Asn Asn Met
275 280

<210> 108
<211> 1835
<212> DNA
<213> Homo sapiens

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<223> n is a, c, g, or t

<400> 108
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<210> 109
<211> 406
<212> PRT
<213> Homo sapiens

<400> 109

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Lys Thr Lys Lys Lys His Phe Val Ala Gln Lys Val Lys Leu Phe Arg
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Ala Ser Asp Pro Leu Leu Ser Val Leu Met Trp Gly Val Asn His Ser
         35                  40                  45

Ile Asn Glu Leu Ser His Val Gln Ile Pro Val Met Leu Met Pro Asp
     50                  55                  60

Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp Asn His Leu Phe Asn
 65                  70                  75                  80

Lys Glu Asn Met Pro Ser His Phe Lys Phe Lys Glu Tyr Cys Pro Met
                 85                  90                  95

Val Phe Arg Asn Cys Gly Lys Arg Phe Gly Ile Asp Val Gln Asp Phe
            100                 105                 110

Gln Asn Ser Leu Thr Arg Ser Ala Pro Leu Pro Asn Asp Ser Gln Ala
        115                 120                 125

Arg Ser Gly Ala Arg Phe His Thr Ser Tyr Asp Lys Arg Tyr Met Ile
    130                 135                 140

Lys Thr Ile Thr Ser Glu Asp Val Ala Glu Met His Asn Ile Leu Lys
145                 150                 155                 160

Lys Tyr His Gln Tyr Ile Val Glu Cys His Gly Ile Thr Leu Leu Pro
                165                 170                 175

His Leu Leu Gly Met Tyr Arg Leu Asn Val Asp Gly Val Glu Ile Tyr
            180                 185                 190
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Val Ile Val Thr Arg Asn Val Phe Ser His Arg Leu Ser Val Tyr Arg
        195                 200                 205

Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg Glu Ala Ser Asp Lys
    210                 215                 220

Glu Lys Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn
225                 230                 235                 240

Glu Gly Gln Lys Ile Tyr Ile Asp Asp Asn Ser Lys Lys Val Phe Leu
                245                 250                 255

Glu Lys Leu Lys Lys Asp Val Glu Phe Leu Ala Gln Leu Lys Leu Met
            260                 265                 270

Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val Glu Arg Ala Glu Gln
        275                 280                 285

Glu Glu Val Glu Cys Glu Glu Asn Asp Gly Glu Glu Glu Gly Glu Ser
    290                 295                 300

Asp Gly Thr His Pro Val Gly Thr Pro Pro Asp Ser Pro Gly Asn Thr
305                 310                 315                 320

Leu Asn Ser Ser Pro Pro Leu Ala Pro Gly Glu Phe Glu Pro Asn Ile
                325                 330                 335

Asp Val Tyr Gly Ile Lys Cys His Glu Asn Ser Pro Arg Lys Glu Val
            340                 345                 350

Tyr Phe Met Ala Ile Ile Asp Ile Leu Thr His Tyr Asp Ala Lys Lys
        355                 360                 365

Lys Ala Ala His Ala Ala Lys Thr Val Lys His Gly Ala Gly Ala Glu
    370                 375                 380

Ile Ser Thr Val Asn Pro Glu Gln Tyr Ser Lys Arg Phe Leu Asp Phe
385                 390                 395                 400

Ile Gly His Ile Leu Thr
                405
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<210> 110
<211> 2572
<212> DNA
<213> Homo sapiens

<400> 110

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gaaatgggca gatgtgggct ccagggcacc cagaattgca ggcttaggag ctaacagcaa 240
ccaggattct gtagtctagc aatcttgctt tacaggtgag gaaactgggc ctagaaaggc 300
gaagtgattt ttttgcctct ctcagcttta ttcctctttt cctctgaact gtagagtcta 360
aagattcagc acaaagcagt tttgtgtagt ggatacataa gctttttttgt tgttattttt 420
ctgaattatt ttgttgactt tcaaagtttt ttttacataa acagtaaatg ctcgttataa 480
aaatttccat taatacagga agtgaaaaaa gtaaaaaact gcaaattgct gttatcctcc 540
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tgactcctcc aataaatgca gaaacttgta tgtctctccc cgacaactgg attatcatat 660
acattattca agcataggct ttagactcag acatatctac atctaatccc agcttatagc 720
taattatttg agtgaccttg gccaagttgt tcatccagtt ttagtctcaa tctccccatg 780
tgtaaaatga aaataataat agtatctacc tggcctggcg tggcggctta tgcctataat 840
cccagccctt tggaagaccg aggctagtgg atcccttgag ctcaggagtt caagaccaac 900
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gcaacctgag caacagagcg ataccttgtt tctgttaaaa caaacaaaca aacaaaatag 1140
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agttcctggt actgatagta gtaagcacta cacacacaca cacacacaca cacacacaca 1260
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tgtgagttgg gagggtgtgg ggcagtgtgg gttggctgga ccagctgttg cttcagagct 1560
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caagagtgta aaggtaagtg aggctcagcc attgggatag aggtggggat gacattgaga 2280
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```

<210> 111
<211> 197
<212> PRT
<213> Homo sapiens

<400> 111

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Met Ala Pro Lys Lys Pro Glu Pro Lys Lys Glu Ala Ala Lys Pro Ala
  1               5                  10                  15

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Glu
             20                  25                  30

Ala Pro Lys Glu Pro Ala Phe Asp Pro Lys Ser Val Lys Ile Asp Phe
         35                  40                  45

Thr Ala Asp Gln Ile Glu Glu Phe Lys Glu Ala Phe Ser Leu Phe Asp
     50                  55                  60

Arg Thr Pro Thr Gly Glu Met Lys Ile Thr Tyr Gly Gln Cys Gly Asp
 65                  70                  75                  80
```

```
Val Leu Arg Ala Leu Gly Gln Asn Pro Thr Asn Ala Glu Val Leu Arg
                 85                  90                  95

Val Leu Gly Lys Pro Lys Pro Glu Glu Met Asn Val Lys Met Leu Asp
            100                 105                 110

Phe Glu Thr Phe Leu Pro Ile Leu Gln His Ile Ser Arg Asn Lys Glu
        115                 120                 125

Gln Gly Thr Tyr Glu Asp Phe Val Glu Gly Leu Arg Val Phe Asp Lys
    130                 135                 140

Glu Ser Asn Gly Thr Val Met Gly Ala Glu Leu Arg His Val Leu Ala
145                 150                 155                 160

Thr Leu Gly Glu Lys Met Thr Glu Ala Glu Val Glu Gln Leu Leu Ala
                165                 170                 175

Gly Gln Glu Asp Ala Asn Gly Cys Ile Asn Tyr Glu Ala Phe Val Lys
            180                 185                 190

His Ile Met Ser Gly
        195
```

<210> 112
<211> 1011
<212> DNA
<213> Homo sapiens

<400> 112
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gatccggtgc agccccagaa ggtcgtggac gcggcgagaa agcacggggt gaaactgacc 180
acagtgctca ccacccacca ccactgggac catgctggcg ggaatgagaa actggtcaag 240
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atcactcacc tgtccacact gcaggtgggg tctctgaacg tcaagtgcct ggcgacccca 360
tgccacactt caggacacat ttgttacttc gtgagcaagc ccggaggctc ggagcccccc 420
gccgtgttca caggtgacac cttgtttgtg gctggctgcg ggaagttcta tgaagggact 480
gcggatgaga tgtgtaaagc tctgctggag gtcttgggcc ggctcccccc ggacacaaga 540
gtctactgtg gccacgagta caccatcaac aacctcaagt ttgcacgcca cgtggagccc 600
ggcaatgccg ccatccggga gaagctggcc tgggccaagg agaagtacag catcggggag 660
cccacagtgc catccaccct ggcagaggag tttacctaca acccccttcat gagagtgagg 720
gagaagacgg tgcagcagca cgcaggtgag acggacccgg tgaccaccat gcgggccgtg 780
cgcagggaga aggaccagtt caagatgccc cgggactgag gccgccctgc accttcagcg 840
gatttgggga ttaggctctt ttaggtaact ggctttcctg ctggtccgtg cgggaaattc 900
agtcttgatt taaccttaat tttacagccc ttggcttgtg ttatcggaca ttctaatgca 960
tatttataag agaagtttaa caagtattta ttcccataaa aaaaaaaaaa a 1011

<210> 113
<211> 260
<212> PRT
<213> Homo sapiens

<400> 113
```
Met Lys Val Glu Val Leu Pro Ala Leu Thr Asp Asn Tyr Met Tyr Leu
  1               5                  10                  15
```

```
Val Ile Asp Asp Glu Thr Lys Glu Ala Ala Ile Val Asp Pro Val Gln
            20                  25                  30

Pro Gln Lys Val Val Asp Ala Ala Arg Lys His Gly Val Lys Leu Thr
        35                  40                  45

Thr Val Leu Thr Thr His His His Trp Asp His Ala Gly Gly Asn Glu
    50                  55                  60

Lys Leu Val Lys Leu Glu Ser Gly Leu Lys Val Tyr Gly Gly Asp Asp
65                  70                  75                  80

Arg Ile Gly Ala Leu Thr His Lys Ile Thr His Leu Ser Thr Leu Gln
                85                  90                  95

Val Gly Ser Leu Asn Val Lys Cys Leu Ala Thr Pro Cys His Thr Ser
            100                 105                 110

Gly His Ile Cys Tyr Phe Val Ser Lys Pro Gly Gly Ser Glu Pro Pro
        115                 120                 125

Ala Val Phe Thr Gly Asp Thr Leu Phe Val Ala Gly Cys Gly Lys Phe
    130                 135                 140

Tyr Glu Gly Thr Ala Asp Glu Met Cys Lys Ala Leu Leu Glu Val Leu
145                 150                 155                 160

Gly Arg Leu Pro Pro Asp Thr Arg Val Tyr Cys Gly His Glu Tyr Thr
                165                 170                 175

Ile Asn Asn Leu Lys Phe Ala Arg His Val Glu Pro Gly Asn Ala Ala
            180                 185                 190

Ile Arg Glu Lys Leu Ala Trp Ala Lys Glu Lys Tyr Ser Ile Gly Glu
        195                 200                 205

Pro Thr Val Pro Ser Thr Leu Ala Glu Glu Phe Thr Tyr Asn Pro Phe
    210                 215                 220

Met Arg Val Arg Glu Lys Thr Val Gln Gln His Ala Gly Glu Thr Asp
225                 230                 235                 240

Pro Val Thr Thr Met Arg Ala Val Arg Arg Glu Lys Asp Gln Phe Lys
                245                 250                 255

Met Pro Arg Asp
            260
```

<210> 114
<211> 2233
<212> DNA
<213> Homo sapiens

<400> 114
agaggggccc cgcgcgcgga tctcgcgaga gcattagagg gcggaagcgc tatccgagca 60
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tcttggccac cgaaagcgtc aagcaagaag aagctggagt acggccttct gcaggaaacg 180
tctccaccca ccccagcttg agccaacggc ctggaggctc taccaagtcg catccggagc 240
cgcagactcc aaaagacagc cctagcaagt cgagtgcgga ggcgcagacc ccagaagaca 300
cccccaacaa gtcgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtcgggtg 360
cggaggcaca gacccccaaa ggcagcacta gcaagtcggg ttcggaggcg cagaccacaa 420
aagacagcac tagtaagtcg catccggagc tgcagactcc aaaagacagc actggcaaat 480
cgggtgcgga ggcgcagacc ccagaagaca gccccaacag gtcgggtgcg gagccaaaga 540
cccaaaaaga cagccctagc aagtcaggtt cggaggcgca gaccacaaaa gatgtcccta 600
ataagtcggg tgcggacggc cagaccccaa aagacggctc cagcaagtcg ggtgcggagg 660
atcagacccc aaaagacgtc cctaacaagt cgggtgcgga gaagcagact ccaaaagacg 720
gctctaacaa gtccggtgca gaggagcagg gcccaataga cgggcccagc aagtcgggtg 780
cggaggagca gacctcaaaa gacagcccta acaaggtggt tccagagcag ccttcccgga 840
aagaccattc caagcccatc tccaaccctt ctgataacaa ggagctcccc aaggctgaca 900
caaaccagct tgctgacaaa gggaagcttt ctcctcatgc tttcaaaacc gaatctgggg 960
aggaaactga cctcatttct cccccgcagg aggaagttaa gtcttcagag cctactgagg 1020
atgtggggcc caaagaggct gaagatgatg atacaggacc cgaggagggc tcaccgccca 1080
aagaagagaa agaaaagatg tccggttctg cctccagtga gaaccgtgaa gggacacttt 1140
cggattccac gggtagcgag aaggatgacc tttatccgaa cggttctgga aatggcagcg 1200
cggagagcag ccacttcttt gcatatctgg tgactgcagc cattcttgtg gctgtcctct 1260
atatcgctca tcacaacaag cggaagatca ttgcttttgt cctggaagga aaaagatcta 1320
aagtcacccg gcggccaaag gccagtgact accaacgttt ggaccagaag atcttttctc 1380
ccccaagtcc taacagaatg gtatattcct ctggaaaaag atgaacgtca ccaatggatt 1440
gtgctgctct cgtttcagct ttgatttttt tgtccttgag aaccttgtcc tccctgctga 1500
tttgtttcta aatcaaaaga aatgaagaaa aaagtactgt gacctgagag acaccctcct 1560
ctagaattta gtggcgggtc tgggctggca gaggtagggg gctgctttgg gctttgcacc 1620
tgcactttgg tgacattgtt cttctgtgtt ccctttattt atgctggtgg cttccatccg 1680
ttctcctctg gggtgagtgg aggggtatat ggaaacacgg ctatgaccaa agggagatcc 1740
cagcctgggc agcctgcgct gctgaccacc ctccctgggg cccgggctct gtaggaaagt 1800
tggtccttga ctgtggcatt gcactctgca ctgtttctct ctgcagacct aggggaaaac 1860
tgcaggtgga agtgcttttc tactaaggcc tcttactttg ggggggatgt gccctacaga 1920
agacatagaa gatggggaaa tgccaatggg caaagagcta ctttgaatac ataattctct 1980
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gacaaagtga atcaacttcc acttagttgt accgagcata aaacagaact tgggcttcct 2160
ggcagtgagg ccactgtccc atcacagatt tttaaaataa atatgatttg aagtagtgtg 2220
atctttcaca caa 2233

<210> 115
<211> 453
<212> PRT
<213> Homo sapiens

<400> 115
Met Arg Phe Val Val Ala Leu Val Leu Leu Asn Val Ala Ala Ala Gly
1 5 10 15

Ala Val Pro Leu Leu Ala Thr Glu Ser Val Lys Gln Glu Glu Ala Gly
20 25 30

Val Arg Pro Ser Ala Gly Asn Val Ser Thr His Pro Ser Leu Ser Gln
35 40 45

Arg Pro Gly Gly Ser Thr Lys Ser His Pro Glu Pro Gln Thr Pro Lys
50 55 60

Asp Ser Pro Ser Lys Ser Ser Ala Glu Ala Gln Thr Pro Glu Asp Thr
65 70 75 80

```
Pro Asn Lys Ser Gly Gly Glu Ala Lys Thr Leu Lys Asp Ser Ser Asn
                  85                  90                  95

Lys Ser Gly Ala Glu Ala Gln Thr Pro Lys Gly Ser Thr Ser Lys Ser
             100                 105                 110

Gly Ser Glu Ala Gln Thr Thr Lys Asp Ser Thr Ser Lys Ser His Pro
         115                 120                 125

Glu Leu Gln Thr Pro Lys Asp Ser Thr Gly Lys Ser Gly Ala Glu Ala
     130                 135                 140

Gln Thr Pro Glu Asp Ser Pro Asn Arg Ser Gly Ala Glu Pro Lys Thr
145                 150                 155                 160

Gln Lys Asp Ser Pro Ser Lys Ser Gly Ser Glu Ala Gln Thr Thr Lys
                 165                 170                 175

Asp Val Pro Asn Lys Ser Gly Ala Asp Gly Gln Thr Pro Lys Asp Gly
             180                 185                 190

Ser Ser Lys Ser Gly Ala Glu Asp Gln Thr Pro Lys Asp Val Pro Asn
         195                 200                 205

Lys Ser Gly Ala Glu Lys Gln Thr Pro Lys Asp Gly Ser Asn Lys Ser
     210                 215                 220

Gly Ala Glu Glu Gln Gly Pro Ile Asp Gly Pro Ser Lys Ser Gly Ala
225                 230                 235                 240

Glu Glu Gln Thr Ser Lys Asp Ser Pro Asn Lys Val Val Pro Glu Gln
                 245                 250                 255

Pro Ser Arg Lys Asp His Ser Lys Pro Ile Ser Asn Pro Ser Asp Asn
             260                 265                 270

Lys Glu Leu Pro Lys Ala Asp Thr Asn Gln Leu Ala Asp Lys Gly Lys
         275                 280                 285

Leu Ser Pro His Ala Phe Lys Thr Glu Ser Gly Glu Glu Thr Asp Leu
     290                 295                 300

Ile Ser Pro Pro Gln Glu Glu Val Lys Ser Ser Glu Pro Thr Glu Asp
305                 310                 315                 320

Val Gly Pro Lys Glu Ala Glu Asp Asp Asp Thr Gly Pro Glu Glu Gly
                 325                 330                 335

Ser Pro Pro Lys Glu Glu Lys Glu Lys Met Ser Gly Ser Ala Ser Ser
             340                 345                 350

Glu Asn Arg Glu Gly Thr Leu Ser Asp Ser Thr Gly Ser Glu Lys Asp
         355                 360                 365

Asp Leu Tyr Pro Asn Gly Ser Gly Asn Gly Ser Ala Glu Ser Ser His
     370                 375                 380
```

```
Phe Phe Ala Tyr Leu Val Thr Ala Ala Ile Leu Val Ala Val Leu Tyr
385                 390                 395                 400

Ile Ala His His Asn Lys Arg Lys Ile Ile Ala Phe Val Leu Glu Gly
                405                 410                 415

Lys Arg Ser Lys Val Thr Arg Arg Pro Lys Ala Ser Asp Tyr Gln Arg
            420                 425                 430

Leu Asp Gln Lys Ile Phe Ser Pro Pro Ser Pro Asn Arg Met Val Tyr
        435                 440                 445

Ser Ser Gly Lys Arg
    450
```

<210> 116
<211> 829
<212> DNA
<213> Homo sapiens

<400> 116
gcggttcgcc ttcaacatgc cggaaccagc gaagtccgct cccgcgccca agaagggctc 60
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ggagagctac tccgtatacg tgtacaaggt gctgaagcag gtccaccccg acaccggcat 180
ctcctctaag gccatgggaa tcatgaactc cttcgtcaac gacatcttcg aacgcatcgc 240
gggtgaggct tcccgcctgg cgcattacaa caagcgctcg accatcacct ccagggagat 300
ccagacggcc gtgcgcctgc tgctgcccgg ggagttggcc aagcacgccg tgtccgaggg 360
caccaaggcc gtcaccaagt acaccagcgc taagtaaact tgccaaggag ggactttctc 420
tggaatttcc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcggt 480
tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt 540
ccacaagcta aagctggcct cttgatctca ttcagattcc aaagagaatc atttacaagt 600
taatttctgt ctccttggtc cattccttct ctttaataat catttactgt tcctcaaaga 660
attgtttaca ttacccatct cctcttttgc tctgagaaag agtatataag cttctgtacc 720
ccactggggg gttggggtaa tattctgtgg tcctcagccc tgtaccttaa taaatttgta 780
tgccttttt tttaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 829

<210> 117
<211> 126
<212> PRT
<213> Homo sapiens

<400> 117
```
Met Pro Glu Pro Ala Lys Ser Ala Pro Ala Pro Lys Lys Gly Ser Lys
  1               5                  10                  15

Lys Ala Val Thr Lys Ala Gln Lys Lys Asp Gly Lys Lys Arg Lys Arg
            20                  25                  30

Ser Arg Lys Glu Ser Tyr Ser Val Tyr Val Tyr Lys Val Leu Lys Gln
        35                  40                  45

Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn
    50                  55                  60

Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg
65                  70                  75                  80
```

Leu Ala His Tyr Asn Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln
85 90 95

Thr Ala Val Arg Leu Leu Leu Pro Gly Glu Leu Ala Lys His Ala Val
100 105 110

Ser Glu Gly Thr Lys Ala Val Thr Lys Tyr Thr Ser Ala Lys
115 120 125

<210> 118
<211> 3858
<212> DNA
<213> Homo sapiens

<400> 118
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cgggagctga ggcgcaggct ggccagagcg tggagaggaa agccctttcc atcctcaagg 120
ccgttgcagg agatgcccgc gagccacctt cgccagcacc acaccggggt gtaatggata 180
ggtaacagag aagacctcgt cccttcctag tcagggcatc agcatgactg agtgcttcct 240
gccccccacc agcagcccca gtgaacaccg cagggtggag catggcagcg ggcttacccg 300
gacccccagc tctgaagaga tcagccctac taagtttcct ggattgtacc gcactggcga 360
gccctcacct ccccatgaca tcctccatga gcctcctgat gtagtgtctg atgatgagaa 420
agatcatggg aagaaaaaag ggaaatttaa gaaaaaggaa aagaggactg aaggctatgc 480
agcctttcag gaagatagct ctggagatga ggcagaaagt ccttctaaaa tgaagaggtc 540
caagggaatc catgttttca agaagcccag cttttctaaa aagaaggaaa aggattttaa 600
aataaaagag aaacccaaag aagaaaagca taaagaagaa aagcacaaag aagaaaaaca 660
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caaacccatt tttggaattc ctttggctga tgcagtagag aggaccatga tgtatgatgg 840
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gctgcgcgtg cagctgcggc tgctccagat gcagcgagcc aaggccgagc agcaggcgca 2040
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aataactatt ttaacccttg agtggcttct ttttaaacca aaaaccgtct ttctttgctt 2520
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<210> 119
<211> 655
<212> PRT
<213> Homo sapiens

<400> 119
Met Thr Glu Cys Phe Leu Pro Pro Thr Ser Ser Pro Ser Glu His Arg
1 5 10 15

Arg Val Glu His Gly Ser Gly Leu Thr Arg Thr Pro Ser Ser Glu Glu
20 25 30

Ile Ser Pro Thr Lys Phe Pro Gly Leu Tyr Arg Thr Gly Glu Pro Ser
35 40 45

Pro Pro His Asp Ile Leu His Glu Pro Pro Asp Val Val Ser Asp Asp
50 55 60

Glu Lys Asp His Gly Lys Lys Lys Gly Lys Phe Lys Lys Lys Glu Lys
65 70 75 80

Arg Thr Glu Gly Tyr Ala Ala Phe Gln Glu Asp Ser Ser Gly Asp Glu
85 90 95

Ala Glu Ser Pro Ser Lys Met Lys Arg Ser Lys Gly Ile His Val Phe
100 105 110

Lys Lys Pro Ser Phe Ser Lys Lys Lys Glu Lys Asp Phe Lys Ile Lys
115 120 125

Glu Lys Pro Lys Glu Glu Lys His Lys Glu Glu Lys His Lys Glu Glu
130 135 140

```
Lys His Lys Glu Lys Lys Ser Lys Asp Leu Thr Ala Ala Asp Val Val
145                 150                 155                 160

Lys Gln Trp Lys Glu Lys Lys Lys Lys Lys Lys Pro Ile Gln Glu Pro
                165                 170                 175

Glu Val Pro Gln Ile Asp Val Pro Asn Leu Lys Pro Ile Phe Gly Ile
            180                 185                 190

Pro Leu Ala Asp Ala Val Glu Arg Thr Met Met Tyr Asp Gly Ile Arg
        195                 200                 205

Leu Pro Ala Val Phe Arg Glu Cys Ile Asp Tyr Val Glu Lys Tyr Gly
    210                 215                 220

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Glu Ala Cys Gly Arg Thr Thr Glu Thr Glu Lys Val Gln Glu Phe Gln
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Ser Asn Arg Val Leu Tyr Val Phe Phe Thr His Val Gln Glu Leu Phe
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Gly Asn Val Val Leu Lys Gln Val Met Lys Pro Leu Arg Trp Ser Asn
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Met Ala Thr Met Pro Thr Leu Pro Glu Thr Gln Ala Gly Ile Lys Glu
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Glu Ile Arg Arg Gln Glu Phe Leu Leu Asn Cys Leu His Arg Asp Leu
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Leu Ala Met Glu Gln Phe Leu Arg Arg Gln Ile Ala Ser Glu Lys Glu
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Glu Ile Glu Arg Leu Arg Ala Glu Ile Ala Glu Ile Gln Ser Arg Gln
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Gln His Gly Arg Ser Glu Thr Glu Glu Tyr Ser Ser Glu Ser Glu Ser
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Glu Ser Glu Asp Glu Glu Glu Leu Gln Ile Ile Leu Glu Asp Leu Gln
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Arg Gln Asn Glu Glu Leu Glu Ile Lys Asn Asn His Leu Asn Gln Ala
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Ile His Glu Glu Arg Glu Ala Ile Ile Glu Leu Arg Val Gln Leu Arg
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Glu Glu Pro Glu Trp Arg Gly Gly Ala Val Gln Pro Pro Arg Asp Gly
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His Glu Ile Tyr Asn Gly Glu Asn Ala Gln Asp Gln Phe Glu Tyr Glu
35 40 45

Leu Glu Gln Ala Leu Glu Ala Gln Tyr Lys Tyr Ile Val Ile Glu Pro
50 55 60

Thr Arg Ile Gly Asp Glu Thr Ala Arg Trp Ile Thr Val Gly Asn Cys
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Leu His Lys Thr Ala Val Leu Ala Gly Thr Ala Cys Leu Phe Thr Pro
85 90 95

Leu Ala Leu Pro Leu Asp Tyr Ser His Tyr Ile Ser Leu Pro Ala Gly
100 105 110

Val Leu Ser Leu Ala Cys Cys Thr Leu Tyr Gly Ile Ser Trp Gln Phe
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Asp Pro Cys Cys Lys Tyr Gln Val Glu Tyr Asp Ala Tyr Lys Leu Ser
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Arg Leu Pro Leu His Thr Leu Thr Ser Ser Thr Pro Val Val Leu Val
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Glu Ile Arg Pro Gly Leu Pro Glu Ser Glu Pro Arg Pro Pro Arg Pro
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Pro Ala Ala Leu Thr Ala Asp Gln Pro Pro Pro Arg Arg Leu Ser Glu
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Thr Thr Thr Thr Leu Pro Gln Ala Pro Thr Glu Ala Ala Ala Ala Ala
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Pro Gln Asp Pro Ala Pro Lys Ser Pro Val Gly Ser Gly Ala Pro Gln
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Ala Ala Ala Pro Ala Pro Ala Ala His Val Ala Gly Asn Pro Gly Gly
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Asp Ala Ala Pro Ala Ala Thr Gly Thr Ala Ala Ala Ala Ser Leu Ala
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Ala Ala Ala Gly Ser Glu Asp Ala Glu Lys Lys Val Leu Ala Thr Lys
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Val Leu Gly Thr Val Lys Trp Phe Asn Val Arg Asn Gly Tyr Gly Phe
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Ile Asn Arg Asn Asp Thr Lys Glu Asp Val Phe Val His Gln Thr Ala
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Ile Lys Lys Asn Asn Pro Arg Lys Tyr Leu Arg Ser Val Gly Asp Gly
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Ala Ala Asp Arg Arg Arg Tyr Arg Arg Gly Tyr Tyr Gly Arg Arg Arg
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Gly Pro Pro Arg Asn Tyr Ala Gly Glu Glu Glu Glu Glu Gly Ser Gly
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Ser Ser Glu Gly Phe Asp Pro Pro Ala Thr Asp Arg Gln Phe Ser Gly
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Ala Arg Asn Gln Leu Arg Arg Pro Gln Tyr Arg Pro Gln Tyr Arg Gln
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Arg Arg Phe Pro Pro Tyr His Val Gly Gln Thr Phe Asp Arg Arg Ser
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Arg Val Leu Pro His Pro Asn Arg Ile Gln Ala Gly Glu Ile Gly Glu
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Arg Asn Pro Thr Tyr Arg Pro Arg Tyr Arg Ser Arg Gly Pro Pro Arg
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cccagacacc gccaggggcc agtgaacctg ctctcagacc ctgagcaagg ggttgaggtg 2340
actggccagt atgagaggga gaaggctggg ttctcatgga tcgaagtgac cttcaagaac 2400
cccctggtat gggttcacgc atcccctgaa cacgtggtgg tgactcggaa ccgaagaagc 2460
tctgcgtaca agtggaagga gacgctattc tcagtgatgc ccggcctgaa gatgaccatg 2520

gacaagacgg gtctcctgct gctcagtgac ccagacaaag tgaccatcgg cctgttgttc 2580
tgggatggcc gtggggaggg gctccggctc cttctgcgtg acactgaccg cttctccagc 2640
cacgttggag ggacccttgg ccagttttac caggaggtgc tctggggatc tccagcagca 2700
tcagatgacg gcagacgcac gctgagggtt cagggcaatg accactctgc caccagagag 2760
cgcaggctgg attaccagga ggggccccg ggagtggaga tttcctgctg gtctgtggag 2820
ctgtagttct gatggaagga gctgtgccca ccctgtacac ttggcttccc cctgcaactg 2880
cagggccgct tctggggcct ggaccaccat ggggaggaag agtcccactc attacaaata 2940
aagaaaggtg gtgtgagcct ggg 2963

<210> 126
<211> 930
<212> PRT
<213> Homo sapiens

<400> 126

```
Met Lys Pro Pro Arg Pro Val Arg Thr Cys Ser Lys Val Leu Val Leu
  1               5                  10                  15

Leu Ser Leu Leu Ala Ile His Gln Thr Thr Thr Ala Glu Lys Asn Gly
             20                  25                  30

Ile Asp Ile Tyr Ser Leu Thr Val Asp Ser Arg Val Ser Ser Arg Phe
         35                  40                  45

Ala His Thr Val Val Thr Ser Arg Val Val Asn Arg Ala Asn Thr Val
     50                  55                  60

Gln Glu Ala Thr Phe Gln Met Glu Leu Pro Lys Lys Ala Phe Ile Thr
 65                  70                  75                  80

Asn Phe Ser Met Asn Ile Asp Gly Met Thr Tyr Pro Gly Ile Ile Lys
                 85                  90                  95

Glu Lys Ala Glu Ala Gln Ala Gln Tyr Ser Ala Ala Val Ala Lys Gly
            100                 105                 110

Lys Asn Ala Gly Leu Val Lys Ala Thr Gly Arg Asn Met Glu Gln Phe
        115                 120                 125

Gln Val Ser Val Ser Val Ala Pro Asn Ala Lys Ile Thr Phe Glu Leu
    130                 135                 140

Val Tyr Glu Glu Leu Leu Lys Arg Arg Leu Gly Val Tyr Glu Leu Leu
145                 150                 155                 160

Leu Lys Val Arg Pro Gln Gln Leu Val Lys His Leu Gln Met Asp Ile
                165                 170                 175

His Ile Phe Glu Pro Gln Gly Ile Ser Phe Leu Glu Thr Glu Ser Thr
            180                 185                 190

Phe Met Thr Asn Gln Leu Val Asp Ala Leu Thr Thr Trp Gln Asn Lys
        195                 200                 205

Thr Lys Ala His Ile Arg Phe Lys Pro Thr Leu Ser Gln Gln Gln Lys
    210                 215                 220
```

```
Ser Pro Glu Gln Gln Glu Thr Val Leu Asp Gly Asn Leu Ile Ile Arg
225                 230                 235                 240

Tyr Asp Val Asp Arg Ala Ile Ser Gly Gly Ser Ile Gln Ile Glu Asn
                245                 250                 255

Gly Tyr Phe Val His Tyr Phe Ala Pro Glu Gly Leu Thr Thr Met Pro
            260                 265                 270

Lys Asn Val Val Phe Val Ile Asp Lys Ser Gly Ser Met Ser Gly Arg
        275                 280                 285

Lys Ile Gln Gln Thr Arg Glu Ala Leu Ile Lys Ile Leu Asp Asp Leu
    290                 295                 300

Ser Pro Arg Asp Gln Phe Asn Leu Ile Val Phe Ser Thr Glu Ala Thr
305                 310                 315                 320

Gln Trp Arg Pro Ser Leu Val Pro Ala Ser Ala Glu Asn Val Asn Lys
                325                 330                 335

Ala Arg Ser Phe Ala Ala Gly Ile Gln Ala Leu Gly Gly Thr Asn Ile
            340                 345                 350

Asn Asp Ala Met Leu Met Ala Val Gln Leu Leu Asp Ser Ser Asn Gln
        355                 360                 365

Glu Glu Arg Leu Pro Glu Gly Ser Val Ser Leu Ile Ile Leu Leu Thr
    370                 375                 380

Asp Gly Asp Pro Thr Val Gly Glu Thr Asn Pro Arg Ser Ile Gln Asn
385                 390                 395                 400

Asn Val Arg Glu Ala Val Ser Gly Arg Tyr Ser Leu Phe Cys Leu Gly
                405                 410                 415

Phe Gly Phe Asp Val Ser Tyr Ala Phe Leu Glu Lys Leu Ala Leu Asp
            420                 425                 430

Asn Gly Gly Leu Ala Arg Arg Ile His Glu Asp Ser Asp Ser Ala Leu
        435                 440                 445

Gln Leu Gln Asp Phe Tyr Gln Glu Val Ala Asn Pro Leu Leu Thr Ala
    450                 455                 460

Val Thr Phe Glu Tyr Pro Ser Asn Ala Val Glu Glu Val Thr Gln Asn
465                 470                 475                 480

Asn Phe Arg Leu Leu Phe Lys Gly Ser Glu Met Val Val Ala Gly Lys
                485                 490                 495

Leu Gln Asp Arg Gly Pro Asp Val Leu Thr Ala Thr Val Ser Gly Lys
            500                 505                 510

Leu Pro Thr Gln Asn Ile Thr Phe Gln Thr Glu Ser Ser Val Ala Glu
        515                 520                 525
```

```
Gln Glu Ala Glu Phe Gln Ser Pro Lys Tyr Ile Phe His Asn Phe Met
    530                 535                 540

Glu Arg Leu Trp Ala Tyr Leu Thr Ile Gln Gln Leu Leu Glu Gln Thr
545                 550                 555                 560

Val Ser Ala Ser Asp Ala Asp Gln Gln Ala Leu Arg Asn Gln Ala Leu
                565                 570                 575

Asn Leu Ser Leu Ala Tyr Ser Phe Val Thr Pro Leu Thr Ser Met Val
            580                 585                 590

Val Thr Lys Pro Asp Asp Gln Glu Gln Ser Gln Val Ala Glu Lys Pro
        595                 600                 605

Met Glu Gly Glu Ser Arg Asn Arg Asn Val His Ser Gly Ser Thr Phe
    610                 615                 620

Phe Lys Tyr Tyr Leu Gln Gly Ala Lys Ile Pro Lys Pro Glu Ala Ser
625                 630                 635                 640

Phe Ser Pro Arg Arg Gly Trp Asn Arg Gln Ala Gly Ala Ala Gly Ser
                645                 650                 655

Arg Met Asn Phe Arg Pro Gly Val Leu Ser Ser Arg Gln Leu Gly Leu
            660                 665                 670

Pro Gly Pro Pro Asp Val Pro Asp His Ala Ala Tyr His Pro Phe Arg
        675                 680                 685

Arg Leu Ala Ile Leu Pro Ala Ser Ala Pro Pro Ala Thr Ser Asn Pro
    690                 695                 700

Asp Pro Ala Val Ser Arg Val Met Asn Met Lys Ile Glu Glu Thr Thr
705                 710                 715                 720

Met Thr Thr Gln Thr Pro Ala Pro Ile Gln Ala Pro Ser Ala Ile Leu
                725                 730                 735

Pro Leu Pro Gly Gln Ser Val Glu Arg Leu Cys Val Asp Pro Arg His
            740                 745                 750

Arg Gln Gly Pro Val Asn Leu Leu Ser Asp Pro Glu Gln Gly Val Glu
        755                 760                 765

Val Thr Gly Gln Tyr Glu Arg Glu Lys Ala Gly Phe Ser Trp Ile Glu
    770                 775                 780

Val Thr Phe Lys Asn Pro Leu Val Trp Val His Ala Ser Pro Glu His
785                 790                 795                 800

Val Val Val Thr Arg Asn Arg Arg Ser Ser Ala Tyr Lys Trp Lys Glu
                805                 810                 815

Thr Leu Phe Ser Val Met Pro Gly Leu Lys Met Thr Met Asp Lys Thr
            820                 825                 830
```

```
Gly Leu Leu Leu Leu Ser Asp Pro Asp Lys Val Thr Ile Gly Leu Leu
        835                 840                 845

Phe Trp Asp Gly Arg Gly Glu Gly Leu Arg Leu Leu Leu Arg Asp Thr
    850                 855                 860

Asp Arg Phe Ser Ser His Val Gly Gly Thr Leu Gly Gln Phe Tyr Gln
865                 870                 875                 880

Glu Val Leu Trp Gly Ser Pro Ala Ala Ser Asp Asp Gly Arg Arg Thr
                885                 890                 895

Leu Arg Val Gln Gly Asn Asp His Ser Ala Thr Arg Glu Arg Arg Leu
            900                 905                 910

Asp Tyr Gln Glu Gly Pro Pro Gly Val Glu Ile Ser Cys Trp Ser Val
        915                 920                 925

Glu Leu
    930
```

<210> 127
<211> 191
<212> PRT
<213> Homo sapiens

<400> 127

```
Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu
  1               5                  10                  15

Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly
             20                  25                  30

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln
         35                  40                  45

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu
     50                  55                  60

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu
 65                  70                  75                  80

Met Arg Cys Gly Gly Cys Ser Asn Asp Glu Gly Leu Glu Cys Val Pro
                 85                  90                  95

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His
            100                 105                 110

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys
        115                 120                 125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly
    130                 135                 140

Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr
145                 150                 155                 160
```

```
Cys Lys Cys Ser Cys Lys Asn Thr His Ser Arg Cys Lys Ala Arg Gln
                165                 170                 175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg
            180                 185                 190


<210> 128
<211> 221
<212> PRT
<213> Homo sapiens

<400> 128
Met Pro Val Met Arg Leu Phe Pro Cys Phe Leu Gln Leu Leu Ala Gly
  1               5                  10                  15

Leu Ala Leu Pro Ala Val Pro Pro Gln Gln Trp Ala Leu Ser Ala Gly
            20                  25                  30

Asn Gly Ser Ser Glu Val Glu Val Val Pro Phe Gln Glu Val Trp Gly
         35                  40                  45

Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu
     50                  55                  60

Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu
 65                  70                  75                  80

Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro
                85                  90                  95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly
            100                 105                 110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys
        115                 120                 125

Glu Cys Arg His Ser Pro Gly Arg Gln Ser Pro Asp Met Pro Gly Asp
    130                 135                 140

Phe Arg Ala Asp Ala Pro Ser Phe Leu Pro Pro Arg Arg Ser Leu Pro
145                 150                 155                 160

Met Leu Phe Arg Met Glu Trp Gly Cys Ala Leu Thr Gly Ser Gln Ser
                165                 170                 175

Ala Val Trp Pro Ser Ser Pro Val Pro Glu Glu Ile Pro Arg Met His
            180                 185                 190

Pro Gly Arg Asn Gly Lys Lys Gln Gln Arg Lys Pro Leu Arg Glu Lys
        195                 200                 205

Met Lys Pro Glu Arg Cys Gly Asp Ala Val Pro Arg Arg
    210                 215                 220


<210> 129
<211> 1356
```

<212> PRT
<213> Homo sapiens

<400> 129

```
Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
  1               5                  10                  15

Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
             20                  25                  30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
         35                  40                  45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
     50                  55                  60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
 65                  70                  75                  80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
                 85                  90                  95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
            100                 105                 110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
        115                 120                 125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
    130                 135                 140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
145                 150                 155                 160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
                165                 170                 175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
            180                 185                 190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
        195                 200                 205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
    210                 215                 220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
225                 230                 235                 240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
                245                 250                 255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
            260                 265                 270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
        275                 280                 285
```

```
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
    290                 295                 300

Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
305                 310                 315                 320

Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met
                325                 330                 335

Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala
            340                 345                 350

Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly
        355                 360                 365

Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr
    370                 375                 380

Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu
385                 390                 395                 400

Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val
                405                 410                 415

Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val
            420                 425                 430

Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr
        435                 440                 445

Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu
    450                 455                 460

Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr
465                 470                 475                 480

Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys
                485                 490                 495

Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys
            500                 505                 510

Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr
        515                 520                 525

Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser
    530                 535                 540

Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln
545                 550                 555                 560

Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser
                565                 570                 575

Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro
            580                 585                 590
```

Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp Thr
595 600 605

Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp Ile
610 615 620

Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp Tyr
625 630 635 640

Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val Val
645 650 655

Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly Asn
660 665 670

Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser Cys
675 680 685

Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp Asn
690 695 700

Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn Arg
705 710 715 720

Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr Thr
725 730 735

Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe Phe
740 745 750

Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ile Ile Ile Leu
755 760 765

Val Gly Thr Ala Val Ile Ala Met Phe Phe Trp Leu Leu Leu Val Ile
770 775 780

Ile Leu Arg Thr Val Lys Arg Ala Asn Gly Gly Glu Leu Lys Thr Gly
785 790 795 800

Tyr Leu Ser Ile Val Met Asp Pro Asp Glu Leu Pro Leu Asp Glu His
805 810 815

Cys Glu Arg Leu Pro Tyr Asp Ala Ser Lys Trp Glu Phe Pro Arg Asp
820 825 830

Arg Leu Lys Leu Gly Lys Pro Leu Gly Arg Gly Ala Phe Gly Gln Val
835 840 845

Ile Glu Ala Asp Ala Phe Gly Ile Asp Lys Thr Ala Thr Cys Arg Thr
850 855 860

Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr His Ser Glu His Arg
865 870 875 880

Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly His His Leu
885 890 895

```
Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gly Gly Pro Leu
            900                 905                 910

Met Val Ile Val Glu Phe Cys Lys Phe Gly Asn Leu Ser Thr Tyr Leu
        915                 920                 925

Arg Ser Lys Arg Asn Glu Phe Val Pro Tyr Lys Thr Lys Gly Ala Arg
    930                 935                 940

Phe Arg Gln Gly Lys Asp Tyr Val Gly Ala Ile Pro Val Asp Leu Lys
945                 950                 955                 960

Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser Gly
                965                 970                 975

Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Glu Ala Pro
            980                 985                 990

Glu Asp Leu Tyr Lys Asp Phe Leu Thr Leu Glu His Leu Ile Cys Tyr
        995                1000                1005

Ser Phe Gln Val Ala Lys Gly Met Glu Phe Leu Ala Ser Arg Lys Cys
   1010                1015                1020

Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Lys Asn
1025                1030                1035                1040

Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp
                1045                1050                1055

Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro Leu Lys Trp Met
            1060                1065                1070

Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr Ile Gln Ser Asp Val
        1075                1080                1085

Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser
   1090                1095                1100

Pro Tyr Pro Gly Val Lys Ile Asp Glu Glu Phe Cys Arg Arg Leu Lys
1105                1110                1115                1120

Glu Gly Thr Arg Met Arg Ala Pro Asp Tyr Thr Thr Pro Glu Met Tyr
                1125                1130                1135

Gln Thr Met Leu Asp Cys Trp His Gly Glu Pro Ser Gln Arg Pro Thr
            1140                1145                1150

Phe Ser Glu Leu Val Glu His Leu Gly Asn Leu Leu Gln Ala Asn Ala
        1155                1160                1165

Gln Gln Asp Gly Lys Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu
   1170                1175                1180

Ser Met Glu Glu Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser
1185                1190                1195                1200
```

```
Cys Met Glu Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn
                1205                1210                1215

Thr Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
            1220                1225                1230

Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu
        1235                1240                1245

Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val Leu
    1250                1255                1260

Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu Ser Pro
1265                1270                1275                1280

Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser Val Ala Ser
                1285                1290                1295

Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser Gly Tyr His Ser Asp
            1300                1305                1310

Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu Ala Glu Leu Leu Lys
        1315                1320                1325

Leu Ile Glu Ile Gly Val Gln Thr Gly Ser Thr Ala Gln Ile Leu Gln
    1330                1335                1340

Pro Asp Ser Gly Thr Thr Leu Ser Ser Pro Pro Val
1345                1350                1355


<210> 130
<211> 98
<212> PRT
<213> Homo sapiens

<400> 130
Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
  1               5                  10                  15

Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
             20                  25                  30

Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
         35                  40                  45

Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
     50                  55                  60

Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
 65                  70                  75                  80

Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg
                 85                  90                  95

Ser Pro
```

<210> 131
<211> 94
<212> PRT
<213> Homo sapiens

<400> 131
Met Ser Val Lys Gly Met Ala Ile Ala Leu Ala Val Ile Leu Cys Ala
1 5 10 15

Thr Val Val Gln Gly Phe Pro Met Phe Lys Arg Gly Arg Cys Leu Cys
20 25 30

Ile Gly Pro Gly Val Lys Ala Val Lys Val Ala Asp Ile Glu Lys Ala
35 40 45

Ser Ile Met Tyr Pro Ser Asn Asn Cys Asp Lys Ile Glu Val Ile Ile
50 55 60

Thr Leu Lys Glu Asn Lys Gly Gln Arg Cys Leu Asn Pro Lys Ser Lys
65 70 75 80

Gln Ala Arg Leu Ile Ile Lys Lys Val Glu Arg Lys Asn Phe
85 90

<210> 132
<211> 5102
<212> DNA
<213> Homo sapiens

<400> 132
gaattccact tctctgtcgc ccgcggttcg ccgccccgct cgccgccgcg atgccagtgt 60
ttcatacgcg cacgatcgag agcatcctgg agccggtggc acagcagatc tcccacctgg 120
tgataatgca cgaggagggc gaggtggacg gcaaagccat tcctgacctc accgcgcccg 180
tggccgccgt gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa 240
ccactgagga tcagattttg aagagagata tgccaccagc atttattaag gttgagaatg 300
cttgcaccaa gcttgtccag gcagctcaga tgcttcagtc agacccttac tcagtgcctg 360
ctcgagatta tctaattgat gggtcaaggg gcatcctctc tggaacatca gacctgctcc 420
ttaccttcga tgaggctgag gtccgtaaaa ttattagagt ttgcaaagga attttggaat 480
atcttacagt ggcagaggtg gtggagacta tggaagattt ggtcacttac acaaagaatc 540
ttgggccagg aatgactaag atggccaaga tgattgacga gagacagcag gagctcactc 600
accaggagca ccgagtgatg ttggtgaact cgatgaacac cgtgaaagag ttgctgccag 660
ttctcatttc agctatgaag atttttgtaa caactaaaaa ctcaaaaaac caaggcatag 720
aggaagcttt aaaaaatcgc aatttttactg tagaaaaaat gagtgctgaa attaatgaga 780
taattcgtgt gttacaactc acctcttggg atgaagatgc ctgggccagc aaggacactg 840
aagccatgaa gagagcattg gcctccatag actccaaact gaaccaggcc aaaggttggc 900
tccgtgaccc tagtgcctcc ccaggggatg ctggtgagca ggccatcaga cagatcttag 960
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cttgcaaaat gctagggcag atgactgatc aagtggctga cctccgtgcc agaggacaag 1080
gatcctcacc ggtggccatg cagaaagctc agcaggtatc tcagggtctg gatgtgctca 1140
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ttgcaaagaa gatcgatgct gctcagaact ggcttgcaga tccaaatggt ggaccggaag 1260
gagaagagca gattcgaggt gctttggctg aagctcggaa aatagcagaa ttatgtgatg 1320
atcctaaaga aagagatgac attctacgtt cccttgggga aatatctgct ctgacttcta 1380
aattagcaga tctacgaaga caggggaaag gagattctcc agaggctcga gccttggcca 1440
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gcagaccggc caaagcagct gtacaccttg agggcaagat tgagcaagca cagcggtgga 1560

ttgataatcc cacagtggat gaccgtggag tcggtcaggc tgccatccgg gggcttgtgg 1620
ccgaagggca tcgtctggct aatgttatga tggggcctta tcggcaagat cttctcgcca 1680
agtgtgaccg agtggaccag ctgacagccc agctggctga cctggctgcc agaggggaag 1740
gggagagtcc tcaggcacga gcacttgcat ctcagctcca agactcctta aaggatctaa 1800
aagctcggat gcaggaggcc atgactcagg aagtgtcaga tgttttcagc gataccacaa 1860
ctcccatcaa gctgttggca gtggcagcca cggcgcctcc tgatgcgcct aacagggaag 1920
aggtatttga tgagagggca gctaactttg aaaaccattc aggaaagctt ggtgctacgg 1980
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cagtgaagac ggcccgagaa ctcacacccc aggtggtctc ggctgctcgt atcttactta 2100
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atgcttcaga agaagcaatt aaaaaagacc tggacaagtg caaggtagct atggccaaca 2280
ttcagcctca gatgctggtt gctggggcaa ccagtattgc tcgtcgggcc aaccggatcc 2340
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aagctgcctc tgatgaattg agcaaaacca tctccccaat ggtgatggat gcaaaagctg 2460
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cgcctccacc agaccttgaa caactccgac taacagatga gcttgctcct cccaaaccac 2640
ctctgcctga aggtgaggtc cctccaccta ggcctccacc accagaggaa aaggatgaag 2700
agttccctga gcagaaggcc ggggaggtga ttaaccagcc aatgatgatg gctgccagac 2760
agctccatga tgaagctcgc aaatggtcca gcaagggcaa tgacatcatt gcagcagcca 2820
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agtatgcttc catcatcctt tttgcacttc aagatactaa aatttcagaa tggaaactag 1200
gactatgtac accagaaaca ctgttttgtt gtgatgttac aaaatataac tccccaacta 1260
atttccagat agatggaaga aatagaaaag tgattatgga cttaaagaca atggaaaatc 1320
ttggacttgc tcaaaattgt actatctcta ttcaggatta tgaagttttt cgatgcgaag 1380
gtaggtttaa ttagataatc ctgtagagag ttctcccttg catgtttggt aggtttgaac 1440
caattcatct ctttaaggaa aaatgaactt ttcacttgtc aataatttgg atgattcaga 1500
ctgaaacctg gatacagatt gtttgctaag agacaaccat ggtcaataaa atgtatattt 1560
atgataagaa cccttaacgt aagatttatc ctcttagcac attttaagta c 1611

<210> 158
<211> 155
<212> DNA
<213> Homo sapiens

<400> 158
gaattcactg atattcattc attcattcag ccaattattc gacaacttct aatctacatt 60
attctttgat tatttcccca gattcactgg atgaaagaaa gataaaaggg gtcattgagt 120
aagtcaatgt ttttaagatt ctattactct cttca 155

<210> 159
<211> 312
<212> DNA
<213> Homo sapiens

<400> 159
tttgcgacct aacctcagtc aattgttaaa aacggtcatg tctaaacagg ctcaggaaga 60
gcttactgtc tgccttgaga acttatgaac catatggatc cctggttcaa caaatacgaa 120
ttctcctcct gggtccaatt ggagctccca agtccagctt tttcaactca gtgaggtctg 180
ttttccaagg gcatgtaacg catcaggctt tggtgggcac taatacaact gggatatctg 240
agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaat caattatatt 300
tcaaaagctt tt 312

<210> 160
<211> 447
<212> DNA
<213> Homo sapiens

<400> 160
ggccacctag cctttgcttc tctgttcaaa tcaattatat ttcaaaagcc ttttgcagat 60
caactttatt acatatagac ttcatctcaa tttataataa aaaatgaatc tttaaaattg 120
cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac 180
ctgccgttta ttctgtgtga ctcactgggg ctgagtgaga aagaaggcgg cctgtgcagg 240
gatgacatat tctatatctt gaacggtaac attcgtgata gataccaggt aatatttgac 300
taatgagaaa ttataactga tttttaaaat gcttatttt gtacaaatgt atcagcgttt 360
atcttcttaa attatacttg ctcaagatcc tttgtctctt ttagattttt tttttcaaaa 420
agaataaaaa catctcgagg gctcttc 447

<210> 161
<211> 341
<212> DNA
<213> Homo sapiens

<400> 161
ttgtgctcat aaatatttgt tgaattaata tcttgcttta tgtctacctt acagtttaat 60
cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac 120
agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctcctctcag 180
atgatagtaa agatcaaaag aattcaaagg gagttggtaa acgctggtga gtctcattcc 240
actttgctaa gggtaatacc actaagggta attgactaga ctgtatttta gaatgctttt 300
tggacaggat aaagaactta agtcattgca tatttcaatc t 341

<210> 162
<211> 288
<212> DNA
<213> Homo sapiens

<400> 162
gatctttcca aatctgaaat tgttccatag gttgcctatt acataattga tagttaaata 60
acttgaaaat actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg 120
tacatgtggc tttgctcact catgtggata gcatggattt gattacaaaa ggtgacctta 180
tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc cttcgtaaac 240
acattttctg gggtatgtta ctacaatcac atactagtgt gtataaaa 288

<210> 163
<211> 372
<212> DNA
<213> Homo sapiens

<400> 163
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actaacataa aataatattt ttcactgttt tgcaatgtct ttttaatttc tgtattgcag 120
ctagaggaag tccaaagaaa acttggattt gctctttctg acatctcggt ggttagcaat 180
tattcctctg agtgggagct ggaccctgta aaggatgttc taattctttc tgctctgaga 240
cgaatgctat gggctgcaga tgacttctta gaggatttgc cttttgagca aataggtaga 300
tggtttggtg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttggatc 360
tattaaatac tg 372

<210> 164
<211> 483
<212> DNA
<213> Homo sapiens

<400> 164
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aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaaggttc 120
acgtaaattt cctcacatca cagaagatta aaattcagaa aggagaaaac acagaccaaa 180
gagaagtatc taagaccaaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata 240
gaacattgta gtacttgtaa ataactagaa ataacatgat ttagtcataa ttgtgaaaaa 300
taataataat ttttcttgga tttatgttct gtatctgtga aaaaataaat ttcttataaa 360
actcgggtct aacttgagag tgtgtgtgat tttggaaaaa ttatgatttg tcagcatctt 420
ctgatattca ctgctttcat cttaattttg ccttctgatt ttatttctaa agtatgtgat 480
ttt 483

<210> 165
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 165
gctctcttat ttgtaccggt ttttg 25

<210> 166
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 166
aagctagtga ctgtcaccga tcag 24

<210> 167
<211> 16
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 167
tcatgtttcc aatctc 16

<210> 168
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 168
cctgatataa atgcaatatt aatgccttta 30

<210> 169
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 169
aagaaccggg agagcaaaca t 21

<210> 170
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 170
atctatgcca aagatcactt 20

<210> 171
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 171
ggagcaccgc ctgtgaa 17

<210> 172
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 172
tgtgcgttgc ctgaatgaac 20

<210> 173
<211> 16

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 173
accaacctga agacac 16

<210> 174
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 174
tctcgactga atggactttg ca 22

<210> 175
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 175
ttgtgtaccc cgcaccaa 18

<210> 176
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 176
cacacctcta tcccggc 17

<210> 177
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 177
gctgcatgtg gatcctgaga 20

<210> 178
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 178
tgagtagcca gaataatcac catca 25

<210> 179
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 179
cttcaagctc ctgggtaa 18

<210> 180
<211> 136
<212> DNA
<213> Homo sapiens

<400> 180
ggtgccgcca gctgccgcac cagcccgaac accattgagg gagctgggag accctcccca 60
cagtgccacc catgcagctg ctccccaggc caccccgctg atggagcccc accttgtctg 120
ctaaataaac atgtgc 136

<210> 181
<211> 1066
<212> PRT
<213> Homo sapiens

<400> 181
Met Pro Val Phe His Thr Arg Thr Ile Glu Ser Ile Leu Glu Pro Val
1 5 10 15

Ala Gln Gln Ile Ser His Leu Val Ile Met His Glu Glu Gly Glu Val
20 25 30

Asp Gly Lys Ala Ile Pro Asp Leu Thr Ala Pro Val Ala Ala Val Gln
35 40 45

Ala Ala Val Ser Asn Leu Val Arg Val Gly Lys Glu Thr Val Gln Thr
50 55 60

Thr Glu Asp Gln Ile Leu Lys Arg Asp Met Pro Pro Ala Phe Ile Lys
65 70 75 80

Val Glu Asn Ala Cys Thr Lys Leu Val Gln Ala Ala Gln Met Leu Gln
85 90 95

```
Ser Asp Pro Tyr Ser Val Pro Ala Arg Asp Tyr Leu Ile Asp Gly Ser
            100                 105                 110

Arg Gly Ile Leu Ser Gly Thr Ser Asp Leu Leu Leu Thr Phe Asp Glu
        115                 120                 125

Ala Glu Val Arg Lys Ile Ile Arg Val Cys Lys Gly Ile Leu Glu Tyr
    130                 135                 140

Leu Thr Val Ala Glu Val Val Glu Thr Met Glu Asp Leu Val Thr Tyr
145                 150                 155                 160

Thr Lys Asn Leu Gly Pro Gly Met Thr Lys Met Ala Lys Met Ile Asp
                165                 170                 175

Glu Arg Gln Gln Glu Leu Thr His Gln Glu His Arg Val Met Leu Val
            180                 185                 190

Asn Ser Met Asn Thr Val Lys Glu Leu Leu Pro Val Leu Ile Ser Ala
        195                 200                 205

Met Lys Ile Phe Val Thr Thr Lys Asn Ser Lys Asn Gln Gly Ile Glu
    210                 215                 220

Glu Ala Leu Lys Asn Arg Asn Phe Thr Val Glu Lys Met Ser Ala Glu
225                 230                 235                 240

Ile Asn Glu Ile Ile Arg Val Leu Gln Leu Thr Ser Trp Asp Glu Asp
                245                 250                 255

Ala Trp Ala Ser Lys Asp Thr Glu Ala Met Lys Arg Ala Leu Ala Ser
            260                 265                 270

Ile Asp Ser Lys Leu Asn Gln Ala Lys Gly Trp Leu Arg Asp Pro Ser
        275                 280                 285

Ala Ser Pro Gly Asp Ala Gly Glu Gln Ala Ile Arg Gln Ile Leu Asp
    290                 295                 300

Glu Ala Gly Lys Val Gly Glu Leu Cys Ala Gly Lys Glu Arg Arg Glu
305                 310                 315                 320

Ile Leu Gly Thr Cys Lys Met Leu Gly Gln Met Thr Asp Gln Val Ala
                325                 330                 335

Asp Leu Arg Ala Arg Gly Gln Gly Ser Ser Pro Val Ala Met Gln Lys
            340                 345                 350

Ala Gln Gln Val Ser Gln Gly Leu Asp Val Leu Thr Ala Lys Val Glu
        355                 360                 365

Asn Ala Ala Arg Lys Leu Glu Ala Met Thr Asn Ser Lys Gln Ser Ile
    370                 375                 380

Ala Lys Lys Ile Asp Ala Ala Gln Asn Trp Leu Ala Asp Pro Asn Gly
385                 390                 395                 400
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Gly Pro Glu Gly Glu Glu Gln Ile Arg Gly Ala Leu Ala Glu Ala Arg
405 410 415

Lys Ile Ala Glu Leu Cys Asp Asp Pro Lys Glu Arg Asp Asp Ile Leu
420 425 430

Arg Ser Leu Gly Glu Ile Ser Ala Leu Thr Ser Lys Leu Ala Asp Leu
435 440 445

Arg Arg Gln Gly Lys Gly Asp Ser Pro Glu Ala Arg Ala Leu Ala Lys
450 455 460

Gln Val Ala Thr Ala Leu Gln Asn Leu Gln Thr Lys Thr Asn Arg Ala
465 470 475 480

Val Ala Asn Ser Arg Pro Ala Lys Ala Ala Val His Leu Glu Gly Lys
485 490 495

Ile Glu Gln Ala Gln Arg Trp Ile Asp Asn Pro Thr Val Asp Asp Arg
500 505 510

Gly Val Gly Gln Ala Ala Ile Arg Gly Leu Val Ala Glu Gly His Arg
515 520 525

Leu Ala Asn Val Met Met Gly Pro Tyr Arg Gln Asp Leu Leu Ala Lys
530 535 540

Cys Asp Arg Val Asp Gln Leu Thr Ala Gln Leu Ala Asp Leu Ala Ala
545 550 555 560

Arg Gly Glu Gly Glu Ser Pro Gln Ala Arg Ala Leu Ala Ser Gln Leu
565 570 575

Gln Asp Ser Leu Lys Asp Leu Lys Ala Arg Met Gln Glu Ala Met Thr
580 585 590

Gln Glu Val Ser Asp Val Phe Ser Asp Thr Thr Thr Pro Ile Lys Leu
595 600 605

Leu Ala Val Ala Ala Thr Ala Pro Pro Asp Ala Pro Asn Arg Glu Glu
610 615 620

Val Phe Asp Glu Arg Ala Ala Asn Phe Glu Asn His Ser Gly Lys Leu
625 630 635 640

Gly Ala Thr Ala Glu Lys Ala Ala Ala Val Gly Thr Ala Asn Lys Ser
645 650 655

Thr Val Glu Gly Ile Gln Ala Ser Val Lys Thr Ala Arg Glu Leu Thr
660 665 670

Pro Gln Val Val Ser Ala Ala Arg Ile Leu Leu Arg Asn Pro Gly Asn
675 680 685

Gln Ala Ala Tyr Glu His Phe Glu Thr Met Lys Asn Gln Trp Ile Asp
690 695 700

```
Asn Val Glu Lys Met Thr Gly Leu Val Asp Glu Ala Ile Asp Thr Lys
705                 710                 715                 720

Ser Leu Leu Asp Ala Ser Glu Glu Ala Ile Lys Lys Asp Leu Asp Lys
                725                 730                 735

Cys Lys Val Ala Met Ala Asn Ile Gln Pro Gln Met Leu Val Ala Gly
            740                 745                 750

Ala Thr Ser Ile Ala Arg Arg Ala Asn Arg Ile Leu Leu Val Ala Lys
        755                 760                 765

Arg Glu Val Glu Asn Ser Glu Asp Pro Lys Phe Arg Glu Ala Val Lys
    770                 775                 780

Ala Ala Ser Asp Glu Leu Ser Lys Thr Ile Ser Pro Met Val Met Asp
785                 790                 795                 800

Ala Lys Ala Val Ala Gly Asn Ile Ser Asp Pro Gly Leu Gln Lys Ser
                805                 810                 815

Phe Leu Asp Ser Gly Tyr Arg Ile Leu Gly Ala Val Ala Lys Val Arg
            820                 825                 830

Glu Ala Phe Gln Pro Gln Glu Pro Asp Phe Pro Pro Pro Pro Pro Asp
        835                 840                 845

Leu Glu Gln Leu Arg Leu Thr Asp Glu Leu Ala Pro Pro Lys Pro Pro
    850                 855                 860

Leu Pro Glu Gly Glu Val Pro Pro Pro Arg Pro Pro Pro Pro Glu Glu
865                 870                 875                 880

Lys Asp Glu Glu Phe Pro Glu Gln Lys Ala Gly Glu Val Ile Asn Gln
                885                 890                 895

Pro Met Met Met Ala Ala Arg Gln Leu His Asp Glu Ala Arg Lys Trp
            900                 905                 910

Ser Ser Lys Gly Asn Asp Ile Ile Ala Ala Ala Lys Arg Met Ala Leu
        915                 920                 925

Leu Met Ala Glu Met Ser Arg Leu Val Arg Gly Gly Ser Gly Thr Lys
    930                 935                 940

Arg Ala Leu Ile Gln Cys Ala Lys Asp Ile Ala Lys Ala Ser Asp Glu
945                 950                 955                 960

Val Thr Arg Leu Ala Lys Glu Val Ala Lys Gln Cys Thr Asp Lys Arg
                965                 970                 975

Ile Arg Thr Asn Leu Leu Gln Val Cys Glu Arg Ile Pro Thr Ile Ser
            980                 985                 990

Thr Gln Leu Lys Ile Leu Ser Thr Val Lys Ala Thr Met Leu Gly Arg
        995                1000                1005
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Thr Asn Ile Ser Asp Glu Glu Ser Glu Gln Ala Thr Glu Met Leu Val
   1010                1015                1020

His Asn Ala Gln Asn Leu Met Gln Ser Val Lys Glu Thr Val Arg Glu
1025                1030                1035                1040

Ala Glu Ala Ala Ser Ile Lys Ile Arg Thr Asp Ala Gly Phe Thr Leu
               1045                1050                1055

Arg Trp Val Arg Lys Thr Pro Trp Tyr Gln
           1060                1065
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<210> 182
<211> 1666
<212> DNA
<213> Homo sapiens

<400> 182
ctccataagg cacaaacttt cagagacagc agagcacaca agcttctagg acaagagcca 60
ggaagaaacc accggaagga accatctcac tgtgtgtaaa catgacttcc aagctggccg 120
tggctctctt ggcagccttc ctgatttctg cagctctgtg tgaaggtgca gttttgccaa 180
ggagtgctaa agaacttaga tgtcagtgca taaagacata ctccaaacct ttccacccca 240
aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaac acagaaatta 300
ttgtaaagct ttctgatgga agagagctct gtctggaccc caaggaaaac tgggtgcaga 360
gggttgtgga gaagtttttg aagagggctg agaattcata aaaaaattca ttctctgtgg 420
tatccaagaa tcagtgaaga tgccagtgaa acttcaagca aatctacttc aacacttcat 480
gtattgtgtg ggtctgttgt agggttgcca gatgcaatac aagattcctg gttaaatttg 540
aatttcagta aacaatgaat agtttttcat tgtaccatga aatatccaga acatacttat 600
atgtaaagta ttatttattt gaatctacaa aaaacaacaa ataatttta aatataagga 660
ttttcctaga tattgcacgg gagaatatac aaatagcaaa attgaggcca agggccaaga 720
gaatatccga actttaattt caggaattga atgggtttgc tagaatgtga tatttgaagc 780
atcacataaa aatgatggga caataaattt tgccataaag tcaaatttag ctggaaatcc 840
tggatttttt tctgttaaat ctggcaaccc tagtctgcta gccaggatcc acaagtcctt 900
gttccactgt gccttggttt ctcctttatt tctaagtgga aaaagtatta gccaccatct 960
tacctcacag tgatgttgtg aggacatgtg gaagcacttt aagttttttc atcataacat 1020
aaattatttt caagtgtaac ttattaacct atttattatt tatgtattta tttaagcatc 1080
aaatatttgt gcaagaattt ggaaaaatag aagatgaatc attgattgaa tagttataaa 1140
gatgttatag taaatttatt ttattttaga tattaaatga tgttttatta gataaatttc 1200
aatcagggtt tttagattaa acaaacaaac aattgggtac ccagttaaat tttcatttca 1260
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gtgttgaatt acggaataat gagttagaac tattaaaaca gccaaaactc cacagtcaat 1440
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tatttaaatg actgcatttt taaatacaag gctttatatt tttaacttta agatgttttt 1560
atgtgctctc caaatttttt ttactgtttc tgattgtatg gaaatataaa agtaaatatg 1620
aaacatttaa aatataattt gttgtcaaag taaaaaaaaa aaaaaa 1666

<210> 183
<211> 99
<212> PRT
<213> Homo sapiens

<400> 183
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Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser
  1               5                  10                  15
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Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu
20 25 30

Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe
35 40 45

Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
50 55 60

Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
65 70 75 80

Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
85 90 95

Glu Asn Ser

<210> 184
<211> 2480
<212> DNA
<213> Homo sapiens

<400> 184
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tttacatagt ggcgcaaact cccttactgc tttggatata aatccaggca ggaggaggta 120
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ccaaaggagt gaattcaggc ccttgtatca ctggcagcag gacgtgacca tggagaagct 240
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tatgccacca agagacaaga caatgagatt ctcatatttt ggtctaagga tataggatac 780
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atcttggggc aggagcagga ttccttcggt gggaactttg aaggaagcca gtccctggtg 1020
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aaggtacctc ccggtttttt acaccgcatg ggccccacgt ctctgtctct ggtacctccc 1260
gctttttttac actgcatggt tcccacgtct ctgtctctgg gcctttgttc ccctatatgc 1320
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agctcgttaa ctatgctggg aaatggtcca aaagaatcag aatttgaggt gttttgtttt 1440
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aactaacacc cagaaaggag aaatgatgtt ataaaaaact cataaggcaa gagctgagaa 1560
ggaagcgctg atcttctatt taattcccca cccatgaccc ccagaaagca ggagcattgc 1620
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tccagagtgc tcatcatcat gtcatagaac tgctgggccc aggtctcctg aaatgggaag 1740
cccagcaata ccacgcagtc cctccacttt ctcaaagcac actggaaagg ccattagaat 1800
tgccccagca gagcagatct gctttttttc cagagcaaaa tgaagcacta ggtataaata 1860
tgttgttact gccaagaact taaatgactg gtttttgttt gcttgcagtg ctttcttaat 1920

tttatggctc ttctgggaaa ctcctcccct tttccacacg aaccttgtgg ggctgtgaat 1980
tctttcttca tccccgcatt cccaatatac ccaggccaca agagtggacg tgaaccacag 2040
ggtgtcctgt cagaggagcc catctcccat ctccccagct ccctatctgg aggatagttg 2100
gatagttacg tgttcctagc aggaccaact acagtcttcc caaggattga gttatggact 2160
ttgggagtga gacatcttct tgctgctgga tttccaagct gagaggacgt gaacctggga 2220
ccaccagtag ccatcttgtt tgccacatgg agagagactg tgaggacaga agccaaactg 2280
gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa 2340
tcagccttgt ctggaaccag atctacacct ggactgccca ggtctataag ccaataaagc 2400
ccctgtttac ttgagtgagt ccaagctgtt ttctgatagt tgctttagaa gttgtgacta 2460
acttctctat gacctttgaa 2480

<210> 185
<211> 224
<212> PRT
<213> Homo sapiens

<400> 185
Met Glu Lys Leu Leu Cys Phe Leu Val Leu Thr Ser Leu Ser His Ala
1 5 10 15

Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
20 25 30

Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
35 40 45

Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
50 55 60

Arg Gly Tyr Ser Ile Phe Ser Tyr Ala Thr Lys Arg Gln Asp Asn Glu
65 70 75 80

Ile Leu Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
85 90 95

Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
100 105 110

His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
115 120 125

Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Lys Gly Tyr Thr
130 135 140

Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe
145 150 155 160

Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu Val Gly Asp Ile Gly Asn
165 170 175

Val Asn Met Trp Asp Phe Val Leu Ser Pro Asp Glu Ile Asn Thr Ile
180 185 190

Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val Leu Asn Trp Arg Ala Leu
195 200 205

Lys Tyr Glu Val Gln Gly Glu Val Phe Thr Lys Pro Gln Leu Trp Pro
210 215 220